FORMULATION AND EVALUATION OF SUSTAINED-RELEASE MATRIX TABLETS OF TIMOLOL MALEATE

A dissertation submitted to

THE TAMILNADU Dr. M.G.R.MEDICAL UNIVERSITY, CHENNAI.

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY

IN PHARMACEUTICS

BY

REG .NO:26091385

Under the guidance of

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Department of Pharmaceutics

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THE ERODE COLLEGE OF PHARMACY & RESEARCH INSTITUTE

ERODE -638112, TAMILNADU.

DEDICATED
TO
My
Beloved Family,
Teachers & Friends

Certificates

The Erode College Of Pharmacy & Research Institute

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CERTIFICATE

This is to certify that the investigation in this thesis entitled **"FORMULATION AND EVALUATION OF SUSTAINED-RELEASE MATRIX TABLETS OF TIMOLOL MALEATE"** submitted to The Tamilnadu Dr. M.G.R. Medical University Chennai. For partial fulfillment of the award of degree of **Master of pharmacy** in pharmaceutics was carried out by **Reg .No.26091385** in the department of pharmaceutics**, The Erode College of pharmacy, Erode,** under my guidance and supervision

This work is original and has not been submitted in part or full to any other degree or diploma of this or any other university.

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ENDORSEMENT BY THE PRINCIPAL

This is to certify that the investigation in this thesis entitled **"FORMULATION AND EVALUATION OF SUSTAINED – RELEASE MATRIX TABLETS OF TIMOLOL MALEATE"** submitted in partial fulfillment of the requirements for the Degree Of **MASTER OF PHARMACY in PHARMACEUTICS** were carried out in the pharmaceutics laboratories of The Erode College Of Pharmacy and Research Institute, Erode by **Regd.No.26091385** under the guidance of **Prof. S.P.Senthil, M.Pharm.,(Ph.D.,), Dept. of Pharmaceutics,** The Erode College Of Pharmacy and Research Institute, Erode.

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DECLERATION

The research work embodied in this dissertation work entitled **"FORMULATION AND EVALUATION OF SUSTAINED – RELEASE MATRIX TABLETS OF TIMOLOL MALEATE "** was carried out by me in the Department of Pharmaceutics, The Erode College of Pharmacy, Erode, under the direct supervision of **Prof. S.P.Senthil, M.Pharm.,(Ph.D.,), Dept. of Pharmaceutics, The Erode College of Pharmacy, Erode – 638 112.**

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The work is original and has not been submitted in part or full for the award of any other Degree or Diploma of this or any other University.

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Thesis

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ABBREVIATIONS

ACE	Angiotensin -Converting Enzyme
BP	British Pharmacopoeia
cm	Centimeter
Conc.	Concentration
cps	Centipoises
CRDDS	Controlled Release Drug Delivery System
$^{\circ}C$	Degree Centigrade
EC	Ethylcellulose
F	Formulation
FTIR	Fourier Transform Infrared Spectroscopy
g	Gram
GIT	Gastrointestinal tract
h	Hour
HCl	Hydrochloric acid
HPMC	Hydroxypropylmethylcellulose
IP	Indian Pharmacopoeia
IPA	Isopropyl alcohol

ISA	Intrinsic sympathomimetic activity
Kg	Kilogram
LD	Lethal Dose
LR	Laboratory Reagent
MCC	Microcrystalline cellulose
mcg	Microgram
MDT	Mean dissolution time
MEC	Minimum Effective Concentration
mg	Milligram
min	Minute
mL	Milliliter
mPa s	Milli Pascal Second
MS	Magnesium Stearate
MSC	Maximum Safe Concentration
n	Diffusion coefficient
N	Normality
nm	Nanometer
No.	Number
PEO	Polyethylene Oxide
PVP	Polyvinylpyrrolidone

RH	Relative Humidity
rpm	Revolutions per minute
SD	Standard Deviation
S. No.	Serial Number
SR	Sustained-Release
TM	Timolol Maleate
USP	United States Pharmacopoeia
UV	Ultraviolet
w/w	Weight by weight
μm	Micrometer
%	Percentage
β	Beta

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Chapter 1

Introduction

1. INTRODUCTION

Most conventional oral drug products, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such *immediate-release products* result in relatively rapid drug absorption and onset of accompanying pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms. In recent years, various modified-release drug products have been developed to control the release rate of the drug and/or the time for drug release.

The term *modified-release drug product* is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized".

Several types of modified-release drug products are recognized (Leon Shargel et al., 2004).

Extended-release drug products: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.

Delayed-release drug products: A dosage form that releases a discrete portion or portions of drug at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

Targeted-release drug products. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

The term *controlled-release drug product* was previously used to describe various types of oral extended-release-rate dosage forms, including sustained-release, sustained-action, prolonged-action, long-action, slow-release, and programmed drug delivery.

1.1. Conventional Drug Delivery System

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption (Robinson, 1987).

As can be seen in the graph (Figure 1), administration of the conventional dosage form by extra vascular route does not maintain the drug level in blood for an extended period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

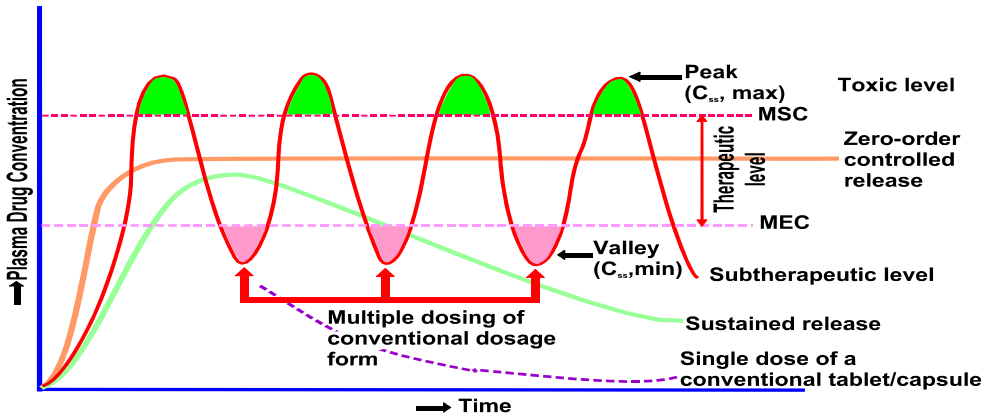


Fig. 1. A hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration).

The conventional dosage forms like solution; suspension, capsule, tablets and suppository etc. have some limitations such as

1) Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.

2) A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range.

3) The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits (Chien, 1992).

1.2. Controlled Release Drug Delivery Systems (CRDDS)

More precisely, controlled delivery can be defined as

1) Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.

2) Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.

3) Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.

4) Provide a physiologically / therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.

A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug. This predetermined rate of drug release is based on the desired therapeutic concentration and the drug's pharmacokinetics.

Advantages of Controlled Drug Delivery System

1. Overcome patient compliance problems.
2. Employ less total drug
    a) Minimize or eliminate local side effects
    b) Minimize or eliminate systemic side effects
    c) Obtain less potentiation or reduction in drug activity with chronic use.
    d) Minimize drug accumulation with chronic dosing.
3. Improve efficiency in treatment
    a) Cures or controls condition more promptly.
    b) Improves control of condition i.e., reduced fluctuation in drug level.
    c) Improves bioavailability of some drugs.
    d) Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.
4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with lesser frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.

Disadvantages

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.

2) Poor *in vitro – in vivo* correlation.

3) Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.

4) Reduced potential for dose adjustment of drugs normally administered in varying strengths (Hoffman, 1998).

1.3. Oral Controlled Drug Delivery Systems

Oral controlled release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action (Vora et al., 1996).

Classification of Oral Controlled Release Systems

A) Diffusion Controlled Systems

I. Reservoir Devices.

A core of drug (the reservoir) surrounded by a polymeric membrane characterizes them. The nature of the membrane determines the rate of drug release.

The characteristics of reservoir diffusion systems are

1. Zero order drug release is possible.
2. The drug release rate is dependent on the type of polymer.

3. High molecular weight compounds are difficult to deliver through the device. Coating and microencapsulation technique can be used to prepare sub devices.

II. Matrix Devices.

It consists of drug dispersed homogeneously in a matrix. The characteristics of the matrix diffusion system is

1. Zero order release cannot be obtained.
2. Easy to produce than reservoir devices.
3. High molecule weight compounds are delivered through the devices.

B) Dissolution controlled systems

I. Matrix Dissolution Controlled System

Aqueous dispersions, congealing, spherical agglomeration etc. can be used.

II. Encapsulation Dissolution Control

Particles, seeds or granules can be coated by technique such as microencapsulation.

C) Diffusion and Dissolution Controlled System.

In a bioerodible matrix, the drug is homogenously dispersed in a matrix and it is released either by swelling controlled mechanism or by hydrolysis or by enzymatic attack.

1.4. Types of Extended-Release Products

General approaches to manufacturing an extended-release drug product include the use of a matrix structure in which the drug is suspended or dissolved, the use of a rate-controlling membrane through which the drug diffuses, or a combination of both. Among the many types of commercial preparations available, none works by a single drug-release mechanism. Most extended-release products release drug by a

combination of processes involving dissolution, permeation, and diffusion. The single most important factor is water permeation, without which none of the product release mechanisms would operate. Controlling the rate of water influx into the product generally dictates the rate at which the drug dissolves. Once the drug is dissolved, the rate of drug diffusion may be further controlled to a desirable rate. Table 1 shows some common extended-release product examples and the mechanisms for controlling drug release, and lists the compositions for some drugs (Leon Shargel, 2004).

Table 1. Examples of Oral Extended-Release Products

Type	Trade Name	Rationale
Erosion tablet	Constant-T	Theophylline
	Tenuate Dospan	Diethylpropion HCl dispersed in hydrophilic matrix
	Tedral SA	Combination product with a slow-erosion component (theophylline, ephedrine HCl) and an initial-release component theophylline, ephedrine HCl, phenobarbital)
Waxy matrix tablet	Kaon *Cl*	Slow release of potassium chloride to reduce GI irritation
Coated pellets in capsule	Ornade spansule	Combination phenylpropanolamine HCl and chlorpheniramine with initial- and extended-release component
Pellets in tablet	Theo-Dur	Theophylline
Leaching	Ferro-Gradumet (Abbott)	Ferrous sulfate in a porous plastic matrix that is excreted in the stool; slow release of iron decreases GI irritation

	Desoxyn gradumet tablet (Abbott)	Methamphetamine methylacrylate methylmethacrylate copolymer, povidone, magnesium stearate; the plastic matrix is porous
Coatedion exchange	Tussionex	Cation ion-exchange resin complex of hydrocodone and phenyltoloxamine
Flotation–diffusion	Valrelease	Diazapam
Osmotic delivery	Acutrim	Phenylpropanolamine HCl (Oros delivery system)
	Procardia-XL	GITS—gastrointestinal therapeutic system with NaCl-driven (osmotic pressure) delivery system for nifedipine
Microencapsulation	Bayer timed-release	Aspirin
	Nitrospan	Microencapsulated nitroglycerin
	Micro-K Extencaps	Potassium chloride microencapsulated particles

1.5. Factors Influencing the Design and Performance of Sustained Release Products

The type of delivery system and route of administration of the drug presented in sustained drug delivery system may depend upon two properties (Bramhankar and Jaiswal, 1995). They are

I. Physicochemical Properties of drugs

II. Biological Factors.

I. Physicochemical Properties of Drugs

1. Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general a single dose of 0.5 to 1gm is considered maximum (Nicholas et al., 1987).

2. Ionization, P^{Ka} & Aqueous Solubility

The pH Partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues. Therefore it is important to note the relationship between the P^{Ka} of the compound and its absorptive environment. For many compounds, the site of maximum absorption will also be the area in which the drug is least soluble.

For conventional dosage forms the drug can generally fully dissolve in the stomach and then be absorbed in the alkaline pH of the intestine. For sustained release formulations much of the drug will arrive in the small intestine in solid form. This means that the solubility of the drug is likely to change several orders of magnitude during its release.

Compounds with very low solubility are inherently controlled, since their release over the time course of a dosage form in the GIT will be limited by dissolution of the drug. The lower limit for the solubility of a drug to be formulated in a sustained release system has been reported to be 0.1mg/mL (Fincher et al., 1968). Thus for slightly soluble drugs, diffusional systems will be poor choice, since the concentration in solution will be low.

For example Tetracycline has maximum solubility in the stomach and least solubility in the intestine where it is maximally absorbed. Other examples of drugs whose incorporation into sustained release systems are limited because of their poor aqueous solubility and slow dissolution rate are digoxin, warfarrin, griseofulvin and

salicylamide. Very soluble drugs are also good candidates for the sustained release dosage forms.

3. Partition coefficient

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability. Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Furthermore partitioning effects apply equally to diffusion through polymer membranes.

4. Drug Stability

The drugs, which are unstable in stomach, can be placed in a slowly soluble form and their release delayed until they reach the small intestine. However, such a strategy would be detrimental for drugs that either are unstable in the small intestine (or) undergo extensive gut wall metabolism, as pointed out in the decrease bioavailability of some anticholinergic drugs from controlled /sustained release formulation. In general the drugs, which are unstable in GIT environment poor candidates for oral sustained release forms.

5. Protein Binding

It is well known that many drugs bind to plasma proteins with a concomitant influence on the duration of drug action. Since blood proteins are mostly recirculated and not eliminated. Drug protein binding can serve as depot for drug producing a prolonged release profile, especially if a high degree of drug binding occurs.

II. Biological Factors

1. Biological Half-Life

Therapeutic compounds with half-life less than 8 hrs are excellent candidates for sustained release preparations. Drugs with very short half-life (less than 2 hrs) will require excessively large amounts of drug in each dosage unit to maintain controlled effects. Thus forcing the dosage form itself to become too large to be administered.

Compounds with relatively long half-lives, generally greater than 8 hrs are not used in the sustained release dosage forms, since their effect is already sustained and also GI transit time is 8-12 hrs (Jantzen et al., 1996). So the drugs, which have long -half life and short half- life, are poor candidates for sustained release dosage forms.

Some examples of drug with half-lives of less than 2 hours are ampicillin, cephalexin, cloxacillin, furosemide, levodopa, penicillin G and propylthiouracil. Examples of those with half-lives of greater than 8 hours are dicumarol, diazepam, digitoxin, digoxin, guanethidine, phenytoin and warfarin.

2. Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Drugs which are absorbed by specialized transport process (carrier mediated) and drug absorption at special sites of the gastrointestinal tract (Absorption Window) are poor candidates for sustained release products.

3. Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained-release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constant(s) for the process(es) are not too large, successful sustained-release products can be developed.

There are two factors associated with the metabolism of some drugs; however that present problems of their use in sustained-release systems. One is the ability of the drug to induce or inhibit enzyme synthesis; this may result in a fluctuating drug blood level with chronic dosing. The other is a fluctuating drug blood level due to intestinal (or other tissue) metabolism or through a hepatic first-pass effect.

Examples of drugs that are subject to intestinal metabolism upon oral dosing are hydralazine, salicylamide, nitroglycerine, isoproterenol, chlorpromazine and levodopa. Examples of drugs that undergo extensive first-pass hepatic metabolism are propoxyphene, nortriptyline, phenacetine, propranolol and lidocaine.

Drugs that are significantly metabolized especially in the region of the small intestine can show decreased bioavailability from slower releasing dosage forms. This is due to saturation of intestinal wall enzyme systems. The drugs should not have intestinal first pass effect and should not induce (or) inhibit metabolism are good candidates for sustained release dosage forms. Various technologies used for controlled release drug delivery systems were given in Table 2 (Chien et al., 1990).

Table 2. Technologies used for CRDDS

S.NO.	DESIGN OR TYPE OF THE SYSTEM	RELEASE MECHANISM
1	**Dissolution Controlled CR systems** • Encapsulation (including Micro encapsulation) - Barrier coating - Embedment into a matrix of fatty materials) - Repeat action coatings - Coated plastic materials or hydrophilic materials Matrix Dissolution Control	The dissolution of drug from system
2	**Diffusion Controlled CR systems** • Reservoir Devices (Fatty polymer coated systems) Matrix Devices (Fatty polymer dispersed systems)	The diffusion of the drug solution through a water - insoluble, permeable polymeric film
3	**Dissolution and Diffusion Controlled CR systems** • Non disintegrating polymeric matrix • Hydrophilic matrices	Diffusion of a drug solution through a porous matrix

4	**Ion- Exchange Resin CR Systems**	Ion- Exchange between the resin - drug complex and ions in the GI tract
5	**pH - Independent formulations**	Influenced by change in pH and ionic permeability of the membrane coating
6	**Osmotically Controlled CR systems**	They contain the buffering agents in a system which maintains constant pH throughout the GIT, so the drug release from the device is not affected by variable pH of GIT. Water entering by Osmosis dissolves the drug, and the drug solution is forced out through a laser drilled orifice
7	**Altered - Density systems**	Diffusion from high - density pellets or from floating

1.6. Monolithic Matrix System

In pharmaceutical CRDDS, matrix based systems are the most commonly used type of release controlling methodology owing to their simple manufacturing process. The preparation of a tablet with the matrix involves the direct compression of the blends of drug, release retardant and other additives, in which the drug is uniformly distribute throughout the matrix core of the release retardant. Alternatively, drug-release retardant blends may be granulated to make the mix suitable for the preparation of tablets by wet granulation or beads (Colombo et al., 1995).

To characterize and define the matrix systems the following properties of the matrix are considered.

1. Chemical nature of the support.
2. The physical state of the drug.
3. The matrix and alteration in volume as the function of the time.

4. The routes of administration.
5. The release kinetics model (in accordance with Higuchi's equation, these system considered to release the drug as a function of square root of time).

The classification of the matrix-based systems is based on the following criteria.

- Matrix structure
- Release kinetics
- Controlled release properties (diffusion, erosion and swelling).
- Chemical nature and the properties of the applied release retardant(s).

Based on the chemical nature of the release retardant(s), the matrix systems are classified as given in Table 3.

Table 3. Classification of Matrix Systems.

Type of the Matrix System	Mechanism
Hydrophilic	- Unlimited swelling delivery by diffusion - Limited swelling controlled delivery eg: Hydroxyethylcellulose, Hydroxypropylmethyl cellulose
Inert	- Inert in nature - Controlled delivery by diffusion eg: Ethylcellulose
Lipidic	- Delivery by diffusion & erosion eg: Carnauba wax.
Biodegradable	- Non lipidic nature - Controlled delivery by surface erosion

Resin Matrices	- Drug release from drug-resin complex eg: Ion exchange resins

1.7. Mechanism of Drug Release from Matrix Tablets

As shown in Figure 2, in erodible matrices, polymer erosion from the surface of the matrix determines the drug release; whilst in hydrophilic matrices, formation of the gel layer and its dynamics as a function of time determines the drug release. Gel layer thickness, which determines the diffusion path length of the drug, corresponds to the distance between the diffusion and erosion fronts. As the swelling process proceeds, the gel layer gradually becomes thicker, resulting in progressively slower drug-release rates; however, due to continuous hydration, polymer disentanglement occurs from the surface of the matrix, resulting in a gradually decreasing depletion zone and an increased dissolution rate.

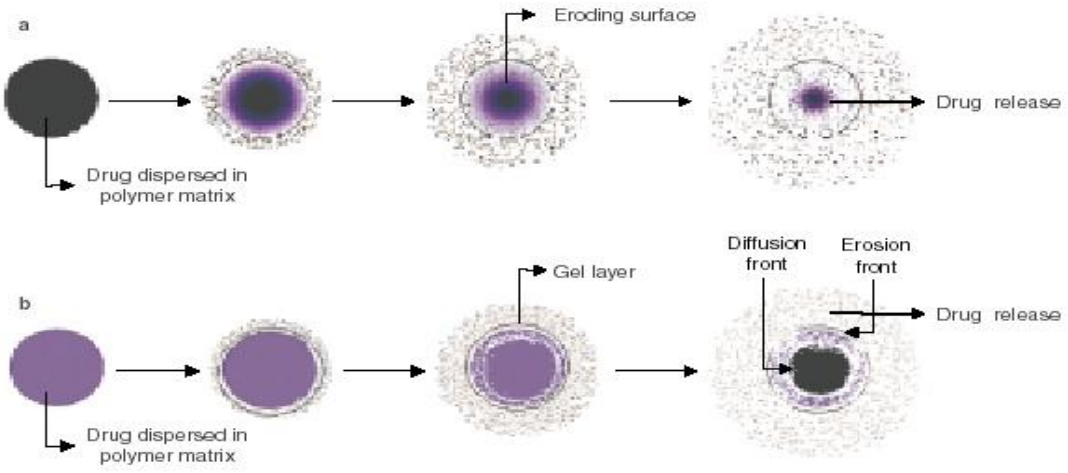


Fig.2. Schematic drug release from matrix diffusion controlled-release drug delivery systems with the drug homogenously dispersed in: (a) an erodible polymer matrix; and (b) a hydrophilic, sellable polymer matrix.

1.8. Drug Release Kinetics -Model Fitting of the Dissolution Data

Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. The pharmaceutical industry and the registration authorities do focus, nowadays, on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q=f(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Hixson–Crowell, Higuchi, Korsmeyer–Peppas models. (Mulye and Turco, 1995; Colombo et al., 1999; Kim et al., 1997; Manthena et al., 2004; Desai et al., 1996; Higuchi et al., 1963).Different models expressing drug release kinetics were given in Table 4

Zero order kinetics

$$Q_1 = Q_0 + K_0 t$$

Where Q_1 is the amount of drug dissolved in time *t*, Q_0 is the initial amount of drug in the solution (most times, Q_0=0) and K_0 is the zero order release constant.

$$f_t = K_0 t$$

Where $f_t = 1-(W_t/W_0)$ and f_t represents the fraction of drug dissolved in time t and K_0 the apparent dissolution rate constant or zero order release constant. In this way, a graphic of the drug-dissolved fraction versus time will be linear if the previously established conditions were fulfilled.

Use: This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc. The pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action.

First order kinetics

Kinetic equation for the first order release is as follows

$$Log\ Q_t = log\ Q_0 + K_1t/2.303$$

Where Q_t is the amount of drug released in time t, Q_0 is the initial amount of drug in the solution and K_1 is the first order release constant. In this way a graphic of the decimal logarithm of the released amount of drug versus time will be linear.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water-soluble drugs in porous matrices, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

$$f_t = K_H t^{1/2}$$

Where K_H is the Higuchi dissolution constant treated sometimes in a different manner by different authors and theories. Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water-soluble drugs.

Hixson–Crowell model

Hixson and Crowell (1931) recognizing that the particle regular area is proportional to the cubic root of its volume derived an equation that can be described in the following manner

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and K_s is a constant incorporating the surface–volume relation. This expression applies to pharmaceutical dosage form such as tablets, where the dissolution occurs in planes

that are parallel to the drug surface if the tablet dimensions diminish proportionally, in such a manner that the initial geometrical form keeps constant all the time.

A graphic of the cubic root of the unreleased fraction of drug versus time will be linear if the equilibrium conditions are not reached and if the geometrical shape of the pharmaceutical dosage form diminishes proportionally over time. This model has been used to describe the release profile keeping in mind the diminishing surface of the drug particles during the dissolution.

Mechanism of Drug Release

To find out the drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix, first 60% drug release data can be fitted in Korsmeyer–Peppas model which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved (Korsmeyer et al., 1983).

$$Log\ (M_t / M_\infty) = Log\ K_{KP} + n\ Log\ t$$

Where, M_t is the amount of drug release at time t, M_∞ is the amount of drug release after infinite time, K_{KP} is a release rate constant incorporating structural and geometrical characteristics of the tablet, and n is the release exponent indicative of the mechanism of drug release.

Table 4. Drug Release Kinetics

Kinetic Model	Relation	Systems Following the Model
First order	$\ln Q_t = \ln Q_o + K_t$ (release is proportional to amount of drug remaining)	Water-soluble drugs in porous matrix
Zero order	$f_t = K_o t$ (independent of drug concentration)	Transdermal systems Osmotic systems
Higuchi	$f_t = K_H t^{1/2}$ (proportional to square root of time)	Matrix formulations

Hixson-Crowell	$W_o^{1/3} - W_t^{1/3} = K_s t$	Erodible isometric matrices

f_t = fraction of dose release at time 't';

K_H, K_o, and K_s = release rate constants characteristic to respective models;

Q_o = the drug amounts remaining to be released at zero hour;

Q_t = the drug amounts remaining to be released at time 't';

W_o = initial amount of drug present in the matrix;

W_t = amount of drug released at time 't'.

1.9. Introduction to Hypertension and Timolol Maleate

Blood pressure is the force of blood pushing against blood vessel walls. The heart pumps blood into the arteries (blood vessels), which carry the blood throughout the body. High blood pressure, also called hypertension, is dangerous because it makes the heart work harder to pump blood to the body and it contributes to hardening of the arteries or atherosclerosis and the development of heart failure.

Hypertension, also referred to as high blood pressure, HTN or HPN, is a medical condition in which the blood pressure is chronically elevated.

There are several categories of blood pressure, including

- Normal: 120/80 mm of Hg
- Prehypertension: 120-139/80-89 mm of Hg
- Stage 1 hypertension: 140-159/90-99 mm of Hg
- Stage 2 hypertension: 160 and above/100 and above

Hypertension can be classified either **essential** (primary) or **secondary**.

Essential hypertension indicates that no specific medical cause can be found to explain a patient's condition. Secondary hypertension indicates that the high blood pressure is a result of (*i.e.*, secondary to) another condition, such as kidney disease or tumours.

The mechanisms and causes of hypertension

The direct mechanisms causing hypertension is one or more of these factors

- An increased tension in the blood vessel walls.
- An increased blood volume caused by elevated levels of salt and lipids in the blood holding back water.
- Hardened and inelastic blood vessels caused by arteriosclerosis.
- The primary causes behind these mechanisms are not fully understood, but these factors contribute to causing hypertension
- A high consume of salt
- A high fat consume.
- Stress at work and in the daily life.
- Smoking.
- Over-weight
- Lack of exercise.
- Kidney failure.

Lifestyle measures to prevent and treat hypertension

Lifestyle measures shall always be a component of the hypertension treatment. Sometimes such measures are enough to cure the condition. Those measures are

- Reducing salt consume.
- Reduction of fat consume, and especially of saturated fat consume.
- Weight reduction.
- Relaxing and stress reduction techniques, for example meditation and autogenic training.
- Regular exercise.

Special food types that reduce the blood pressure

Research projects suggest that the following food types reduce blood pressure.

- Fish oil and fat fish. The working substances seem to be the omega-3 unsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The effect from fish oil seems to cease when the fish oil supplements are stopped.
- Olive oil, especially olive oil of the quality extra virgin.

Natural supplements to help against hypertension

Natural supplements to treat hypertension exist. These supplements reduce blood pressure by lowering the cholesterol and lipid content in the blood, by preventing oxidation of tissue components by free radicals, and by helping damaged blood vessels to heal. Examples of ingredients having these effects are vitamin B3, inositol, turmenic extract and gum guggul extract.

They may also contain Ingredients giving a direct anti-hypertensive effect, like potassium, magnesium, calcium, vitamin C and fatty acids from marine sources.

Medical treatment of hypertension

When lifestyle measures and supplements are not enough to cure the condition, medical treatment must be applied. Many different types of drugs are used, alone or in combination with other drugs, to treat high blood pressure. The major categories are

- ***Angiotensin-converting Enzyme (ACE) Inhibitors:*** ACE inhibitors work by preventing a chemical in the blood, angiotensin I, from being converted into a substance that increases salt and water retention in the body. These drugs also make blood vessels relax, which further reduces blood pressure.
- ***Angiotensin II Receptor Antagonists*****:** These drugs act at a later step in the same process that ACE inhibitors affect. Like ACE inhibitors, they lower blood pressure by relaxing blood vessels.

- ***Beta blockers:*** Beta blockers affect the body's response to certain nerve impulses. This, in turn, decreases the force and rate of the heart's contractions, which lowers blood pressure.
- ***Blood Vessel Dilators (Vasodilators):*** These drugs lower blood pressure by relaxing muscles in the blood vessel walls.
- ***Calcium Channel Blockers:*** Drugs in this group slow the movement of calcium into the cells of blood vessels. This relaxes the blood vessels and lowers blood pressure.
- ***Diuretics:*** These drugs control blood pressure by eliminating excess salt and water from the body.
- ***Nerve Blockers***: These drugs control nerve impulses along certain nerve pathways. This allows blood vessels to relax and lowers blood pressure.

Beta blockers

Beta blockers differ by which receptors are blocked.

First generation beta blockers such as propranolol (Inderal, InnoPran), nadolol (Corgard), timolol maleate (Blocadren), penbutolol sulfate (Levatol), sotalol hydrochloride (Betapace), and pindolol (Visken) are non-selective in nature, meaning that they block both beta$_1$ (β_1) and beta$_2$ (β_2) receptors and will subsequently affect the heart, kidneys, lungs, gastrointestinal tract, liver, uterus, vascular smooth muscle, and skeletal muscle and as an effect, could cause reduced cardiac output, reduced renal output amongst other actions.

Second generation beta blockers such as metoprolol (Lopressor, Toprol XL), acebutolol hydrochloride (Sectral), bisoprolol fumarate (Zebeta), esmolol hydrochloride (Brevibloc), betaxolol hydrochloride (Kerlone), and acebutolol

hydrochloride (Sectral) are selective, as they block only β_1 receptors and as such will affect mostly the heart and cause reduced cardiac output.

Beta blockers such as pindolol (Visken), penbutolol sulfate (Levatol), and acebutolol hydrochloride (Sectral) differ from other beta blockers as they possess intrinsic sympathomimetic activity (ISA), which means they mimic the effects of epinephrine and norepinephrine and can cause an increase in blood pressure and heart rate. ISA's have smaller effects in reducing resting cardiac output and resting heart rate, in comparison to drugs that do not possess ISA.

Beta blocker such as propranolol (Inderal, InnoPran), acebutolol hydrochloride (Sectral), and betaxolol hydrochloride (Kerlone) possess a quinidine-like or anesthetic-like membrane action, which affects cardiac action potential (electrical impulses within the heart that cause contractions).

Beta blockers such as labetalol hydrochloride (Trandate, Normodyne) and carvedilol (Coreg) have both β- and α_1-adrenergic receptors. Blocking the α_1-adrenergic receptors in addition to the β blocker lowers blood pressure which provides additional vasodilatory action of the arteries.

Chapter 2

Review of Literatures

REVIEW OF LITERATURE

2.1. Matrix Formers

Avachat et al., (2007) have studied the effect of different concentrations of hydroxypropylmethylcellulose (HPMC K100CR) on the simultaneous release of both diclofenac sodium (DS) and chondroitin sulphate (CS). They revealed that HPMC K 100CR at a concentration of 40% of the dosage form weight was able to control the simultaneous release of both DS and CS for 9hours.

Krishnan et al., (2007) have prepared sustained release tablets of theophylline using tamarind seed polysaccharide as release retardant. The release of drug from these matrices was found to occur by swelling controlled mechanism obeying first order kinetics.

Nair et al., (2007) have made an attempt to formulate a controlled-release matrix tablet formulation for alfuzosin hydrochloride by using low viscous hydroxypropylmethylcellulose (HPMC K-100 and HPMC 15cps) and its comparison with marketed product. Drug release from the matrix tablets was carried out for 12 hr and showed that the release rate was not highly significant with different ratios of HPMC K-100 and HPMC15cps. They concluded that the use of low viscous hydrophilic polymer of different grades (HPMC K-100 and HPMC 15cps) can control the alfuzosin release for a period of 12 hr and were comparable to the marketed product.

Raslan et al., (2006) have studied the effect of HPMC (hydrophilic) and glyceryl behenate (hydrophobic) polymers on controlled release of anhydrous theophylline matrix tablets and studied *invitro* release characteristics and kinetics of prepared formulations for explaining the release pattern from matrix tablets.

Atul Kuksal et al., (2006) have prepared extended-release matrix tablets of zidovudine using hydrophilic eudragit RLPO and RSPO alone and their combination with hydrophobic ethylcellulose (EC). The in-vitro drug release study revealed that either eudragit preparation was able to sustain the drug release for 6h.Combining eudragit with EC sustained the drug release for 12 h.

Hamid et al., (2006) have formulated & evaluated a once-daily tablet of cefpodoxime using HPMC K4M. They revealed that 35% w/w of HPMC controlled the cefpodoxime proxetil release effectively for 24hours.

Jaleh et al., (2006) have developed sustained-release matrix tablets of highly water-soluble tramadol HCl using natural gums like xanthan gum and guar gum alone or in combination with HPMC. They concluded that guar gum alnoe cannot efficiently control drug release, and xanthan gum has higher drug retarding ability than guar gum. The combination of each natural gum with HPMC leads to a greater retarding effect compared with a mixture of two natural gums.

Saleh et al., (2005) have studied the effect of different viscosity grades LM (30% w/w), MM (40% w/w), HM (50% w/w) of guar gum on the drug release pattern of water-soluble diltiazem hydrochloride. They found that high molecular weight (50% w/w) grade guar gum was able to control the drug release patterns in-vitro and in-vivo.

Vidhyadhara et al., (2004) have revealed that the HPMC K4M along with electrolytes can be used as aids to controlled delivery in the formulation of water soluble drugs like propranolol HCl from tablet matrix.

Jaber et al., (2004) have shown that 15% w/w of carbopol or sodium carboxymethylcellulose or 35% w/w of HPMC K100M can be useful to sustain the release of lithium carbonate from matrix tablet over 8 hours.

Sandip et al., (2003) have studied the effect of concentration of hydrophilic (HPMC) and hydrophobic (hydrogenated castor oil [HCO], EC) on the release rate of tramadol HCl. Tablets prepared by combination of hydrophilic and hydrophobic polymers failed to produce the drug release beyond 12 h. HCO matrix tablets were found to be best suited for modulating the delivery the highly water-soluble drug, tramadol HCl.

Selim et al., (2003) have done the comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. They revealed that the drug release from plastic and hydrophobic matrix was

less than hydrophilic polymer. Again, the release pattern of drug from hydrophilic matrices was closer to zero-order kinetics than that from other classes of matrices.

Maggi et al., (2000) have compared the performance of polyethylene oxide (PEO) and HPMC polymers when employed in the geomatrix technology. They have shown that slower release rates can be obtained from the plain matrices containing HPMC compared to PEO.

Nath et al., (1999) have discussed the use of combination of aliphatic alcohol (cetyl alcohol) and methylcellulose as a sustained release matrix using theophylline as a model drug. They have shown that 30% w/w total matrix component gave extended release of theophylline for more than 8hours.

Pillay et al., (1999) have studied the interaction between drug and electrolyte(s) to control the release of highly water soluble diltiazem hydrochloride from oral hydrophilic monolithic systems. They have used hydrophilic polymers like HPMC and PEO. Electrolytes such as sodium bicarbonate or pentasodium tripolyphosphate were used to modulate intragel pH dynamics, swelling kinetics, and gel properties. They concluded that the dynamics of swelling and gel formation in the presence of ionizable species within hydrophilic matrices provide an attractive alternative for zero-order drug delivery from a simple monolithic system.

Bhalla et al., (1998) have prepared controlled release tablets of carbamazepine using HPMC and EC as release retardants and performed in-vitro & in-vivo studies. They found that EC based formulation was found to be more stable and compared well with the innovator's product.

Kim et al., (1997) have developed a new ternary polymeric matrix system using pectin, HPMC and gelatin to deliver a highly soluble drug like diltiazem HCl over long periods of time. They mentioned that this system offers a number of advantages over existing systems, including ease of manufacturing and of release modulation, as well as reproducibility of release profiles.

2.2. Formulation and Process Variables

Hiremath et al., (2008) have formulated hydrophilic controlled release matrix tablets of rifampicin, a poorly soluble drug, using hydroxypropyl methylcellulose (HPMC) polymer (low, medium, and high viscosity) by direct compression method. Influence of formulation variables and process parameters such as drug:HPMC ratio, viscosity grade of HPMC, drug particle size, and compression force on the formulation characters and drug release has been studied. Their results indicated that the release rate of the drug and the mechanism of release from the HPMC matrices are mainly controlled by the drug:HPMC ratio and viscosity grade of the HPMC. In general, decrease in the drug particle size decreased the drug release. Lower viscosity HPMC polymer was found to be more sensitive to the effect of compression force than the higher viscosity.

Ravi et al., (2008) have designed oral controlled release (CR) matrix tablets of zidovudine (AZT) using HPMC, EC and cabopol-971P (CP) and studied the effect of various formulation factors on in vitro drug release. . Release rate decreased with increase in polymer proportion and compression force. The release rate was lesser in formulations prepared using CP (20%) as compared to HPMC (20%) as compared to EC (20%). No significant difference was observed in the effect of pH of dissolution media on drug release from formulations prepared using HPMC or EC, but significant difference was observed in CP based formulations. Decrease in agitation speed from 100 to 50 rpm decreased release rate from HPMC and CP formulations but no significant difference was observed in EC formulations. Mechanism of release was found to be dependent predominantly on diffusion of drug through the matrix than polymer relaxation incase of HPMC and EC formulations, while polymer relaxation had a dominating influence on drug release than diffusion incase of CP formulations. Designed CR tablets have shown an initial release of 17-25% in first hour and extending the release up to 16-20 hours.

Roberts et al., (2007) have studied the release profiles of aspirin from hypromellose matrices in hydro-ethanolic media. Percent aspirin released increased with increasing levels of ethanol in the dissolution media, correlating with the drug's solubility, however, dose dumping of aspirin did not occur. An initial rapid release

was observed in media comprising 40% ethanol. Release in these conditions was considered to be both erosion and diffusion-mediated, in contrast to the release in 0, 10, 20 and 30% ethanol media, where erosion-controlled release dominated. Image analysis of matrix swelling indicated a slower initial interaction between ethanol and hypromellose accounting for the initial rapid release. Cloud point studies suggested that ethanol retarded hydration of the polymer.

Sinju et al., (2004) have described the effects of temperature and humidity on tablets containing kollidon® SR using diphenhydramine HCl as a model drug. Exposure of tablets to accelerated stability condition (40°C/75%RH) in an open dish resulted in rapid increases in tablet hardness, accompanied by step-wise decreases in dissolution rate. But exposure to 25°C/60%RH similarly resulted in increases in tablet hardness, although with minimal impact on dissolution. Exposure of kollidon® SR tablets to the aqueous coating process indeed resulted in noticeable changes in both hardness and dissolution. Application of the opadry solution appears to affect tablet behavior to a lesser degree, compared to water, most likely due to protection via formed barrier film. Therefore the authors concluded that attention needs to be paid to the extreme sensitivity of kollidon® SR matrix tablets to temperature and moisture during product development.

Silvina et al., (2002) have developed HPMC matrix tablets of diclofenac sodium, evaluated the relationship and influence of different content levels of microcrystalline cellulose (MCC), starch, and lactose, in order to achieve a zero-order release. They found that each of these compounds was capable of interacting to some extent with each other to control drug release.

Paul et al., (1995) have investigated the effects of lubricant magnesium stearate at different concentrations, mixing shear rate, and mixing times on the tablet properties and drug dissolution from controlled release matrix tablets containing HPMC K4M. Diphenhydramine HCl and hydrochlorothiazide were chosen as the model drugs**.** Spray –dried hydrous lactose (Fast-Flo Lactose) and anhydrous dibasic calcium phosphate (A-TAB) were chosen as the model fillers. Tablets containing A-TAB, which compacts via a brittle fracture mechanism, were harder and had significantly better friability patterns than those prepared using Fast Flo Lactose. The

compaction of Fast Flo Lactose appears to be a combination of brittle fracture and plastic deformation. Mixes containing lower levels of lubricant (0.2%) generated tablets that had higher crushing strengths than those with higher lubricant levels (2.0%). Drug release was impacted to the greatest extent by the solubility of the drug and excipients/filler but was only slightly affected by the level of magnesium stearate and duration of mixing.

Chapter 3

Research Envisaged

RESEARCH ENVISAGED

3.1. Objective

- The present work is aimed at preparing and evaluating sustained-release (SR) matrix tablets of timolol maleate (TM) using different polymers
- To study the effect of nature (hydrophilic, hydrophobic and plastic) of the polymer and drug:polymer ratio (1:0.5, 1:1, 1:1.5, and 1:2) on the rate of drug release.
- To study the effect of different diluents (Microcrystalline cellulose (MCC), lactose) on drug release rate.
- To study the effect of method of preparation of tablets (wet granulation and direct compression) on the rate of drug release**.**

3.2. Scope of Work

Timolol maleate is a non-selective beta-adrenergic receptor blocker used in the treatment of essential hypertension, glaucoma, migraine, and for prophylaxis after myocardial infraction. It is rapidly and nearly completely (about 90%) absorbed from the gastrointestinal tract (GIT) following oral ingestion, showing 60% bioavailability. Detectable plasma levels occur within one-half hour and peak plasma levels occur in about 1-2 hours. A plasma half-life is 4 hours. In the treatment of hypertension the usual initial dosage is 10 mg twice a day, whether used alone or added to diuretic therapy. Dosage may be increased or decreased depending on heart rate and blood pressure response. The usual total maintenance dosage is 20-40 mg per day. Increases in dosage to a maximum of 60 mg per day divided into two doses may be necessary (Thomson et al., 2006).

Although conventional tablets of timolol maleate available in the market commercially, no study has been done so far for preparing the timolol maleate sustained-release tablets. To improve the oral bioavailability and to reduce the dose dependent toxicity there is a need for the development of sustained-release formulations. Many patent technologies also indicated that timolol maleate is suitable for the sustained-release (Gregory et al., 2004; Mandana et al., 2000).

The most commonly used method of modulating the drug release is to include it in a matrix system (Salsa et al., 1997).An effort was therefore made to develop simple and effective sustained-release timolol maleate tablets using a polymer matrix system. The drug is freely soluble in water and hence judicious selection of matrix formers is essential for achieving constant release. HPMC is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems (Colombo et al., 1993).Upon contact with the gastrointestinal fluid, HPMC swells, gels, and finally dissolves slowly (Siepmann et al., 1999). The gel becomes a viscous layer acting as a protective barrier to both the influx of water and the efflux of the drug in solution (Colombo et al., 2000; Kiil et al., 2003). As the proportion of the polymer in the formulation increases, the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix (Ford et al., 1985). The dissolution can be either disentanglement or diffusion controlled depending on the molecular weight and thickness of the diffusion boundary layer. The rate of polymer swelling and dissolution as well as the corresponding rate of drug release are found to increase with either higher levels of drug loading or with use of lower viscosity grades of HPMC (Narasimhan et al.,1997). However, the use of hydrophilic matrix former alone for sustaining drug release for highly water soluble drugs is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drugs it is necessary to include hydrophobic polymers in the matrix system (Liu et al., 2001).

Hence, in the present study, an attempt has been made to develop the sustained-release matrix tablets of TM using hydrophilic HPMC K100M CR in combination with hydrophobic ethylcellulose, and the sustained pattern of timolol maleate was evaluated by in-vitro drug release for 12 hours. The drug release data were plotted using various kinetic equations (zero-order, first-order, Higuchi's kinetics, Korsmeyer's equation, and Hixson-Crowell cube root law) to evaluate the drug release mechanism and kinetics. In-vivo drug release, biopharmaceutical evaluation, and in-vitro/in-vivo correlations were beyond the scope of this study and will be considered in future work.

3.3. Plan of The Work

To achieve the objectives of the work, the following work was planned and undertaken:

1) Drug Selection

2) Literature Survey

3) Preformulation Study

Compatability evaluation was carried out between drug and polymers in physical observation and by using infrared spectral study.

4) Construction of the calibration curve for timolol maleate in 0.1N HCl and 6.8 pH phosphate buffer.

5) Calculation of the dose and to construct theoretical release profile of timolol maleate from sustained –release formulations.

6) Preparation of SR formulations of TM using Microcrystalline cellulose as a diluent, following polymers at different concentrations and combinations by wet granulation technique or direct compression.

HPMC K15M

Polyethylene oxide

HPMC K100M CR

Ethylcellulose

Kollidon-SR

7) Selection of the best batch of tablets based on the in-vitro release studies and similarity factor analysis.

8) By using the composition of selected batch, tablets will be prepared by direct compression method and will be evaluated.

9)To perform swelling and erosion studies, FTIR studies, and stability studies for the optimized formulation.

10) The following evaluation parameters were studied based on laboratory experiments.

A. Evaluation of blends

A) Angle of repose

B) Apparent bulk density

C) Tapped bulk density

D) Percent compressibility

E) Hausener's ratio

B. Evaluation of tablets

a) Tablet description

b) Tablet thickness and diameter

c) Hardness

d) Friability

e) Weight variation

f) Content uniformity of active ingredient

g) *In vitro* dissolution study

h) The results of drug release will be studied for zero order of release, Higuchi's classical diffusion equation and kosmeyer's peppa's equation.

i) Similarity Factor (f_2) Analysis

j) Swelling and erosion studies

k) FTIR Studies

l) Optimization of the formulation

m) Accelerated stability study of optimized formulation.

Chapter 4

Drug Profile

Drug Profile

TIMOLOL MALEATE

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent. It possesses an asymmetric carbon atom in its structure and is provided as the levo isomer.

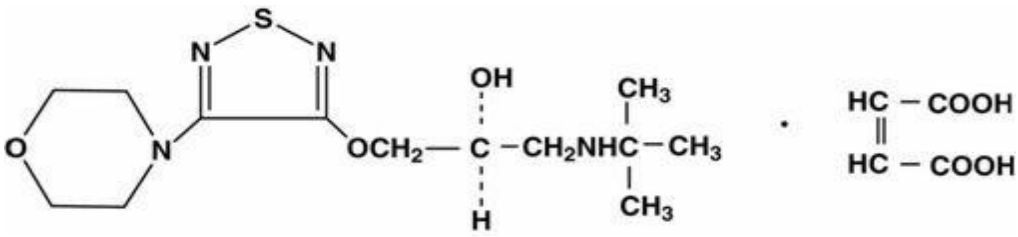
4.1. Description

Nomenclature

- **Generic Name:** Timolol Maleate
- **Chemical Name:** (*S*)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)-1,2,5-thiadiazol-3-yl]oxy]-2-propanol (*Z*)-2-butenedioate (1:1) salt.
- **Trade Names:** Blocadren, Betim, Timoster, Betimol, Novo-Timol, Timoptic.

Formula

- **Empirical Formula:** $C_{13}H_{24}N_4O_3S.C_4H_4O_4$
- **Structural Formula**



Physical and Chemical Properties

- **Molecular weight** - 432.50.
- **Color** - White
- **Nature** - Crystalline powder

- **Odour** - Odourless
- **Melting point** - 201.5-202.5 °C
- **Solubility** - Freely soluble in water; soluble in ethanol and methanol. Sparingly soluble in chloroform, practically insoluble in ether and cyclohexane.
- **pKa** - 3.9

4.2. Pharmacokinetics

Timolol maleate is rapidly and nearly completely absorbed (about 90%) following oral ingestion. Detectable plasma levels of timolol occur within one-half hour and peak plasma levels occur in about one to two hours. The drug half-life in plasma is approximately 4 hours and this is essentially unchanged in patients with moderate renal insufficiency. The absolute bioavailability after oral administration has been reported to be approximately 60%. Timolol is not extensively bound to plasma proteins; i.e., < 10% by equilibrium dialysis and approximately 60% by ultrafiltration. It is extensively (80%) metabolized in liver via the cytochrome P450 2D6 isoenzyme, the metabolites being excreted in urine together with some unchanged timolol. Plasma levels following oral administration are about half those following intravenous administration indicating approximately 50% first pass metabolism. It crosses the placenta and appears in breast milk.

4.3. Pharmacology

i) Indications and Dosage

- **Hypertension:** The usual initial dosage of timolol maleate is 10 mg twice a day, whether used alone or added to diuretic therapy. Dosage may be increased or decreased depending on heart rate and blood pressure response. The usual total maintenance dosage is 20 to 40 mg per day. Increases in dosage to a maximum of 60 mg per day divided into two doses may be necessary. There should be an interval of at least 7 days between increases in dosages.

Timolol maleate tablets may be used with a thiazide diuretic or with other antihypertensive agents. Patients should be observed carefully during initiation of such concomitant therapy.

- **Myocardial Infarction:** The recommended dosage for long-term prophylactic use in patients who have survived the acute phase of a myocardial infarction is 10 mg given twice daily.

- **Migraine:** The usual initial dosage of timolol maleate is 10 mg twice a day. During maintenance therapy the 20 mg daily dosage may be administered as a single dose. Total daily dosage may be increased to a maximum of 30 mg, given in divided doses, or decreased to 10 mg once per day, depending on clinical response and tolerability. If a satisfactory response is not obtained after 6 to 8 weeks use of the maximum daily dosage, therapy with timolol should be discontinued.

- **Glaucoma:** Ophthalmic Solution is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma**.**

ii) Contraindications

Timolol maleate is contraindicated in patients with bronchial asthma or with a history of bronchial asthma, or severe chronic obstructive pulmonary disease sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to this product.

iii) Mechanism of Action

Mechanism of action like propranolol and nadolol, timolol competes with adrenergic neurotransmitters such as catecholamines for binding at beta(1)-adrenergic receptors in the heart and vascular smooth muscle and beta(2)-receptors in the bronchial and vascular smooth muscle. Beta(1)-receptor blockade results in a decrease in resting and exercise heart rate and cardiac output, a decrease in both systolic and diastolic blood pressure, and, possibly, a reduction in reflex orthostatic hypotension. Beta (2)-blockade results in an increase in peripheral vascular resistance. The exact mechanism whereby timolol reduces ocular pressure is still not known. The most likely action is by decreasing the secretion of aqueous humor.

iv) Drug Interaction :

Timolol has some interactions with the drugs like catecholamine-depleting drugs such as reserpine, non-steroidal anti-inflammatory drugs, calcium antagonists, digitalis, quinidine and clonidine.

v) Adverse Effects

Fatigue, bradycardia, nausea, dizziness, bronchial spasm, pruritis. But it is usually well tolerated in properly selected patients. Most adverse effects have been mild & transient.

VI) Precautions

Timolol maleate has been detected in human milk. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Safety and effectiveness in pediatric patients have not been established.

VII) Toxicity

LD_{50}=1190 mg/kg (oral, mice)

LD_{50}=900 mg/kg (oral, rat).

4.4. Pharmacodynamics

Timolol maleate is a beta1 and beta2 (nonselective) adrenergic receptor blocking agent that does not have significant intrinsic sympathomimetic, direct myocardial depressant, or local anesthetic activity. Clinical pharmacology studies have confirmed the beta-adrenergic blocking activity as shown by (1) changes in resting heart rate and response of heart rate to changes in posture; (2) inhibition of isoproterenol-induced tachycardia; (3) alteration of the response to the valsalva maneuver and amyl nitrite administration; and (4) reduction of heart rate and blood pressure changes on exercise. Timolol decreases the positive chronotropic, positive inotropic, bronchodilator, and vasodilator responses caused by beta-adrenergic receptor agonists.

Clinical studies indicate that timolol maleate at a dosage of 20 to 60 mg/day reduces blood pressure without causing postural hypotension in most patients with essential hypertension. Administration of timolol to patients with hypertension results initially in a decrease in cardiac output, little immediate change in blood pressure, and an increase in calculated peripheral resistance. With continued administration of timolol, blood pressure decreases within a few days, cardiac output usually remains reduced, and peripheral resistance falls toward pretreatment levels. Plasma volume may decrease or remain unchanged during therapy with timolol. In the majority of patients with hypertension timolol also decreases plasma renin activity. Dosage adjustment to achieve optimal antihypertensive effect may require a few weeks. When therapy with timolol is discontinued, the blood pressure tends to return to pretreatment levels gradually. In most patients the antihypertensive activity of timolol is maintained with long-term therapy and is well tolerated.

4.5. Method of analysis

- Spectroscopy like-IR, NMR, Mass and UV-Visible Spectroscopy.
- Thin Layer Chromatography
- High Performance Liquid Chromatography

4.6. Storage

Tablets should be stored at 20° to 25°C (68° to 77°F), protected from light. Dispense in a well-closed, light-resistant container.

4.7. Official preparations

- **IP, 1996:** Timolol Maleate eye drops.

  Timolol Maleate tablets.

- **BP, 1993:** Timolol eye drops, Timolol tablets.

- **USP/NF, 2004:** Timolol Maleate & Hydrochlorthiazide tablets.

  Timolol Maleate opthalmic solution.

  Timolol Maleate tablets.

4.8. Proprietary Formulations:

- ***Opthalmic solutions*** **:** Timol (India)

  Timoptic 0.25%, 0.5% (USA)

- ***Tablets :*** Timostar 10mg, 20mg (Mankind Pharma, India)

  Blocadren 5 mg, 10 mg, 20 mg (Merck & Co., USA)

  Betim (UK)

Chapter 5

Polymer and Excipient Profile

5 .POLYMER AND EXCIPIENT PROFILE

The following are the different polymers and excipients used in this work (Raymond et al., 2003)

5.1. Hypromellose

Hypromellose is a partly *O*-methylated and *O*-(2- hydroxypropylated) cellulose.

Synonyms **:** Benecel MHPC; Hydroxypropylmethylcellulose (HPMC); Methocel; Metolose; Tylopur.

Description **:** Odorless and tasteless, white or creamy-white fibrous or granular powder.

Grades **:** Methocel K100 Premium LVEP, Methocel K4M, K15M,K100M,Metolose 60SH, 65SH, 90SH.

Stability **:** Stable material, although it is hygroscopic after drying.

Acidity/alkalinity **:** pH = 5.5–8.0 for a 1% w/w aqueous solution

Density (true) **:** 1.326 g/cm^3.

Melting point **:** Browns at 190–200°C; chars at 225–230°C. Glass transition temperature is 170–180°C.

Viscosity **:** Ranges from 3-100000 mPa s.

Methocel K100M (100000 mPa s),

Methocel K15M (15000 mPa s),

Methocel K4M (4000 mPa s).

Safety **:** Non-toxic and non-irritant material, although excessive oral consumption may have a laxative effect.

Uses **:** As a tablet binder (2% - 5% w/w),

Matrix former (10% - 80% w/w),

Thickening agent (0.45% - 1% w/w),

It is also used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.

5.2. Polyethylene Oxide

Polyethylene oxide as a nonionic homopolymer of ethylene oxide, represented by the formula $(CH_2CH_2O)n$, where *n* represents the average number of oxyethylene groups. It may contain up to 3% of silicon dioxide.

Synonyms **:** Polyox; Polyoxirane; Polyoxyethylene.

Description **:** White to off-white, free-flowing powder, slightly ammonical odour.

Functional Category **:** Mucoadhesive; Tablet binder; Thickening agent

Grades **:** WSR N-10, WSR N-80, WSR N-750, WSR N-3000, WSR 205, WSR 1105, SR N-60K, WSR 301, WSR coagulant, WSR 303.

Solubility **:** Soluble in water and a number of common organic solvents such as acetonitrile, chloroform, and methylene chloride. It is insoluble in aliphatic hydrocarbons, ethylene glycol, and most alcohols.

Angle of Repose **:** 34°

Density (true) **:** 1.3 g/cm^3

Melting Point **:** 65–70°C

Storage Conditions **:** Store in tightly sealed containers in a cool, dry place. Avoid exposure to high temperatures since this can result in reduction in viscosity.

Safety **:** Low level of toxicity regardless of the route of administration. The resins are neither skin irritants nor sensitizers, and they do not cause eye irritation.

Incompatibilities **:** It is incompatible with strong oxidizing agents.

Uses **:** As a tablet binder at a concentration of 5-85%, hydrophilic matrix former, mucoadhesive polymer as effective thickener.

5.3. Ethylcellulose

Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydroglucose units joined together by acetal linkages.

Synonyms **:** Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Description **:** It is a tasteless, free-flowing, white to light tan-colored powder.

Functional Category **:** Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

Solubility **:** It is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%).Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

Density (bulk) **:** 0.4 g/cm^3

Viscosity **:** 7 to 100 mPa s

Stability and Storage **:** It is a stable, slightly hygroscopic material. It should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Safety **:** It is generally regarded as a nontoxic, nonallergenic, and nonirritating material. It is not metabolized following oral consumption and is therefore a noncalorific substance.

Uses **:** It is used in the microencapsulation (10-20% w/w).

As a sustained-release tablet coating (3-20% w/w).

It can be used for tablet coating and tablet granulation (1- 3% w/w).

5.4. Kollidon® SR

Polyvinylacetate/Povidone based polymer (Kollidon® SR) is a relatively new extended release matrix excipient. It consists of 80% Polyvinylacetate and 19% Povidone in a physical mixture, stabilized with 0.8% sodium lauryl sulfate and 0.2% colloidal silica. (BASF, 1999; Ruchatz, 1999)

Description **:** It is a tasteless, free-flowing, non-hygroscopic, white powder.

Functional Category **:** Direct compressible grade sustained release matrix former.

Angle of Repose : 21°

Bulk Density : 0.37 g/mL

Tapped Density : 0.44 g/mL

Hausner's Ratio : 1.13

Mean Particle Size : Approx. 100 μm

Uses : It can be easily applied for controlled release properties by direct compression.

It favours the development and manufacture of Sustained release tablets by its high dry binding capacity and the superb flow properties.

It offers a reliable sustained release characteristic independent of the drug used.

By applying low compression force floating tablets with longer residence time in the stomach can be achieved.

Floating times exceeding 24 hours can be achieved easily.

5.5. Microcrystalline cellulose

Microcrystalline cellulose is purified, partially depolymerized cellulose.

Synonyms **:** Avicel PH; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.

Description **:** It occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

Grades **:** Avicel PH-101, PH-102, PH-103; *Emcocel 50M, 90M; Vivapur 101, 102.*

Functional Category **:** Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Solubility **:** Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Melting point **:** Chars at 260-270°C.

Stability and Storage **:** It is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Safety **:** It is a relatively nontoxic and nonirritant material.

Uses **:** It is widely used as a diluent (20 – 90 %w/w).

As a tablet disintegrant (5-15% w/w).

It can be used as an adsorbent, antiadherent (20- 90%w/w).

5.6. Lactose monohydrate

Lactose monohydrate as a natural disaccharide, obtained from milk, which consists of one galactose and one glucose moiety.

Synonyms **:** Lactochem, Pharmatose, NF Lactose, Capsulac, Granulac, Tablettose, Inhalac, Prismalac, Sachelac.

Description **:** White to off-white crystalline particles or powder, odorless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

Functional Category **:** Binding agent; diluent for dry-powder inhalers; tablet binder; tablet and capsule diluent.

Grades **:** Lactochem powder, coarse powder, fine powder; Pharmatose 50M, 80M, 90M, 100M, Inhalac 70, 120, 230; Lactose monohydrate NF 80M.

Solubility **:** Soluble in water (1 in 5.24), practically insoluble in chloroform, ethanol and ether.

Angle of repose **:** 33° for Pharmatose DCL 15;

32° for Tablettose 70 and Tablettose 80.

Melting point **:** 201–202°C (for dehydrated α-lactose monohydrate)

Density (true) **:** 1.545 g/cm^3 (α-lactose monohydrate)

Safety **:** Adverse reactions to lactose are largely attributed to lactose intolerance, which occurs in individuals with a deficiency of the intestinal enzyme lactase. This results in lactose being undigested and may lead to cramps, diarrhea, distension, and flatulence.

Incompatibilities **:** A Maillard-type condensation reaction is likely to occur between lactose and compounds with a primary amine group to form brown, or yellow-brown-colored products. Lactose is also incompatible with amino acids, aminophylline, amfetamines, and lisinopril.

Stability **:** Mold growth may occur under humid conditions (80% relative humidity and above). Lactose may develop a brown coloration on storage, the reaction being accelerated by warm, damp conditions.

Storage **:** It should be stored in a well-closed container in a cool, dry place.

Uses **:** Widely used as a filler or diluent in tablets and capsules, and to a more limited extent in lyophilized products and infant formulas. It is also used as a diluent in dry-powder inhalation.

5.7. Povidone

Synonyms **:** E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.

Grades **:** PVP K-12, K-15, K-17, K-25, K-30, K-60, K-90, K-120.

Functional Category **:** Disintegrant; dissolution aid; suspending agent; tablet binder.

Description **:** It occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

Melting point **:** Softens at 150°C.

Solubility **:** Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K-value.

Stability and Storage **:** Povidone darkens to some extent on heating at 150°C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110–130°C; steam sterilization of an aqueous solution does not alter its properties. Aqueous solutions are susceptible to mold growth and consequently require the addition of suitable preservatives.

It may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities **:** It is compatible in solution with a wide range of inorganic salts, natural and synthetic resins, and other chemicals. It forms molecular

adducts in solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds; the efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

Safety **:** When consumed orally, povidone may be regarded as essentially nontoxic since it is not absorbed from the gastrointestinal tract or mucous membranes. It additionally has no irritant effect on the skin and causes no sensitization.

Uses **:** In tableting, povidone solutions (0.5-5% w/v) are used as binders in wet-granulation processes. It is also added to powder blends in the dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. It is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. Povidone solutions may also be used as coating agents. It is additionally used as a suspending, stabilizing, or viscosity-increasing agent in number of topical and oral suspensions and solutions. The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Chapter 6

Methodology

6.METHODOLOGY

The materials used in the present investigation were either AR/LR grade or the best possible Pharma grade.

MATERIALS USED

S.NO	MATERIAL	SUPPLIED BY
1	Timolol maleate	Neuland Laboratories,Hyderabad.
2	HPMC K 15 M	Neuland Laboratories,Hyderabad.
3	HPMC K 100 M	Neuland Laboratories,Hyderabad.
4	Polyethylene Oxide	Loba Chemie Pvt. Ltd, Mumbai.
5	Ethyl cellulose	Loba Chemie Pvt. Ltd, Mumbai.
6	Kollidon-SR	Neuland Laboratories,Hyderabad
7	Micro crystalline cellulose	Loba Chemie Pvt. Ltd, Mumbai.
8	Polyvinyl pyrrolidone	Loba Chemie Pvt. Ltd, Mumbai.
9	Isopropyl alcohol	Loba Chemie Pvt. Ltd, Mumbai.
10	Magnesium state	S.D Fine Chem Ltd.,Mumbai
11	Talc	S.D Fine Chem Ltd.,Mumbai

EQUIPMENTS USED

Details of Equipments Used

S. No.	Instrument	Manufacturer
1.	Electronic Weighing Balance	Sartorious bt 2235, Japan.
2.	Tap Density Tester (U.S.P.)	Electrolab, ETD-1020, India.
3.	Sieves	Rolex standard sieves, India.
4.	Tablet punching machine	Cadmach-cmd4
5.	Dissolution Apparatus (U.S.P.)	Distek –2100c
6.	Dissolution sampler	HPLC Waters 2666
7.	Mill	Quardo
8.	pH Meter	L I 120, Elico Pvt. Ltd, India.
9.	Loss on drying tester	Sartorious102
10.	Hardness Tester	Varian-vk200
11.	UV Spectrophotometer	Varian 21cfr-11
12.	Electromagnetic Sieve Shaker	EMS – 8

IDENTIFICATION TESTS:

1) U V spectra :

Dilute the 100 mg of drug sample in phosphate buffer PH 6.8 and UV spectrum is obtained using a 1cm cell and scanning from 200 to 400nm. And compare the λ max value with the standard uv spectrum of Timolol maleate.

2) I R spectra:

The FT-IR spectrum of pure Timolo maleate and physical mixture of Timolol maleate , HPMC K 100 M and Ethyl cellulose were analyzed for compatibility study.

6.1. Construction of Standard Graph of Timolol Maleate

Accurately weigh the amount of 100 mg timolol maleate was transferred into a 100ml volumetric flask. 20 ml of 0.1N hydrochloric acid (HCl) was added to dissolve the drug and volume was made up to 100 mL with the same HCl. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 mL with 0.1N HCl which has given the solution having the concentration of 100 mcg/mL. Necessary dilutions were made by using this second solution to give the different concentrations of timolol maleate (5 to 50 mcg/mL) solutions.

The absorbances of above solutions were recorded at λ_{max} (295 nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis).

Similarly, standard graph was plotted with 6.8 pH phosphate buffer.

Preparation of 0.1 N HCl: Accurately measured 8.5 mL of concentrated hydrochloric acid was added to 1000 mL of distilled water.

Preparation of pH 6.8 phosphate buffer: Accurately measured 50 mL of 0.2 M potassium dihydrogen orthophosphate was transferred to a 200mL volumetric flask and 22.4 mL of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 mL with distilled water, mixed and pH was adjusted to 6.8 with 0.2 M sodium hydroxide or 0.2 M othophosphoric acid.

Preparation of 0.2 M potassium dihydrogen phosphate solution: Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 mL of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

6.2. Calculation of Sustained-Release Dose and Theoretical Release Profile of Timolol Maleate

The total dose of timolol maleate for twice-daily SR formulation was calculated by Robinson Eriksen (Robinson and Eriksen, 1966) equation using available pharmacokinetic data.

The zero-order drug release rate constant (k_0) was calculated using following equation

$$k_0 = DI \times k_e$$

Where DI is the initial dose (i.e., conventional dose = 10 mg) and k_e is first-order rate constant for overall elimination.

$$k_e = 0.693 / t_{1/2}$$

Where $t_{1/2}$ = Biological half-life of timolol maleate = 4 h

Therefore $k_e = 0.693 / 4$

$= 0.1732$ mg/h.

Availability rate $R = k_e \times DI$

$= 0.1732 \times 10$

$= 1.732$ mg/h.

Loading dose = $D_L = DI - R \times t_{max}$

where t_{max} = 2 h

Therefore D_L = 10-(1.732 x 2)

= 6.54 mg.

Maintenance dose = D_M = R x H

where H = Number of hours for which sustained action is desired after initial release.

Therefore D_M = 1.732 x 11

= 19.05 mg.

Total dose required = $D_T = D_L + D_M$

= 6.54+19.05

= 25.59 mg

≅25 mg

Hence an oral controlled release formulation of timolol maleate should contain a total dose of 25 mg and should release 6.54 mg in first 1 hour like conventional tablets, and 1.73 mg/h up to 12 hours thereafter.

6.3. Preparation of Timolol Maleate Matrix Tablets

All the matrix tablets, each containing 25 mg of timolol maleate, were prepared by wet granulation method and some of the formulations were prepared by direct compression method also to study the effect of method of manufacture on the drug release.

Wet granulation: Drug and the diluent (MCC or Lactose) were sifted through sieve No. 40 manually and mixed well to ensure the uniformity of premix blend. Several drug-diluent premixes were then mixed with the selected ratio of polymer(s), previously sifted through sieve No. 40, for 5 minutes. Premix blend was wet granulated with 5% w/v solution of PVP K-90 in a mortar. The wet mass was passed through No.18 sieve. The wet granules were dried at 55°C ± 5°C for 1 hour in a hot-air oven and the dried granules were sieved through No.22 sieve.

These granules were blended with lubrication mixture (1% w/w magnesium stearate and 2% w/w talc) and compressed using 16 station rotary tableting machine, equipped with flat-faced, round punches of 6-mm diameter.

Direct compression: Accurately weighed amounts of drug, polymer, and diluent were mixed geometrically in a mortar. This mixture was passed through No.40 sieve and thoroughly mixed in a polythene bag for 15 minutes. The powder blend was then lubricated with magnesium stearate and talc for 2 minutes and compressed into tablets on a 16-station rotary tableting machine using 6-mm round, flat-faced punches.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 120mg with different drug polymer ratios like 1:0.5, 1:1, 1:1.5, 1:2. The various polymers used were HPMC K15M, Polyethylene oxide, Kollidon-SR, HPMC K100M CR and Ethyl cellulose. Diluents like MCC (water-insoluble) or lactose (water soluble) were used for the preparation of matrix tablets.

Table 5. List of Different Formulations

Formulae	Polymer (s)	Diluent	Method
F1 to F4	HPMC K15M	MCC	Wet granulation
F5 to F8	Polyethylene oxide	MCC	Wet granulation
F9 to F12	HPMC K 100M	MCC	Wet granulation
F13 to F16	Ethyl cellulose	MCC	Wet granulation
F17 to F20	Kollidon-SR	MCC	Direct compression
F21 to F25	HPMC K100M & EC	MCC	Wet granulation
F26 to F30	HPMC K 100M &HPMC K 15M	MCC	Wet granulation

6.4. Formulations

In the formulations prepared, the release retardants included were hydroxypropylmethylcellulose (HPMC K15M, HPMC K100M CR), polyethylene oxide (PEO), ethylcellulose (EC), and Kollidon-SR. Microcrystalline cellulose (MCC), lactose were used as diluents. Magnesium stearate (MS) 1% and talc 2 % were used as lubricants. 5% w/v solution of polyvinylpyrrolidone (PVP-K90) in isopropyl alcohol (IPA) was used as binder. Compositions of different formulations were given in the following Tables (Table 6 to Table 12).

Table 6. Composition of Matrix Tablets Containing HPMC K15M*

F.Code	TM (mg)	HPMC K15M (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F1	25	12.5	72.9	6	qs	1.2	2.4	120
F2	25	25	60.4	6	qs	1.2	2.4	120
F3	25	37.5	47.9	6	qs	1.2	2.4	120
F4	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F1, F2, F3, and F4 respectively.

Table 7. Composition of Matrix Tablets Containing Polyethylene Oxide

F.Code	TM (mg)	PEO (mg)	MCC (mg)	PVP-K90 (mg)	IPA (ml)	MS (mg)	Talc (mg)	Total (mg)
F5	25	12.5	72.9	6	qs	1.2	2.4	120
F6	25	25	60.4	6	qs	1.2	2.4	120
F7	25	37.5	47.9	6	qs	1.2	2.4	120
F8	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F5, F6, F7, and F8 respectively.

Table 8. Composition of Matrix Tablets Containing HPMC K100M CR*

F.Code	TM (mg)	HPMC K 100M (mg)	MCC (mg)	PVP-K90 (mg)	IPA (ml)	MS (mg)	Talc (mg)	Total (mg)
F9	25	12.5	72.9	6	qs	1.2	2.4	120
F10	25	25	60.4	6	qs	1.2	2.4	120
F11	25	37.5	47.9	6	qs	1.2	2.4	120
F12	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F9, F10, F11, and F12 respectively.

Table 9. Composition of Matrix Tablets Containing Ethylcellulose*

F.Code	TM (mg)	EC (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F13	25	12.5	72.9	6	qs	1.2	2.4	120
F14	25	25	60.4	6	qs	1.2	2.4	120
F15	25	37.5	47.9	6	qs	1.2	2.4	120
F16	25	50	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F13, F14, F15, and F16 respectively.

Table 10. Composition of Matrix Tablets Containing Kolliodon-SR*

F.code	TM (mg)	Kollidon-SR (mg)	MCC (mg)	PVP-K90 (mg)	MS (mg)	Talc (mg)	Total (mg)
F17	25	12.5	72.9	6	1.2	2.4	120
F18	25	25	60.4	6	1.2	2.4	120
F19	25	37.5	47.9	6	1.2	2.4	120
F20	25	50	35.4	6	1.2	2.4	120

* Drug to Polymer ratio is 1:0.5, 1:1, 1:1.5, and 1:2 for F17, F18, F19, and F20 respectively.

Table 11. Composition of Matrix Tablets Containing Combination of HPMC K100M and EC*

F.Code	TM (mg)	HPMC K100M (mg)	EC (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F21	25	40	10	35.4	6	qs	1.2	2.4	120
F22	25	30	20	35.4	6	qs	1.2	2.4	120
F23	25	25	25	35.4	6	qs	1.2	2.4	120
F24	25	20	30	35.4	6	qs	1.2	2.4	120
F25	25	10	40	35.4	6	qs	1.2	2.4	120

* qs = quantity sufficient; Drug to Polymer ratio is 1:2; HPMC to EC ratio is 4:1, 3:2, 1:1, 2:3, and 1:4 for F21, F22, F23, F24, and F25 respectively.

Table 12. Composition of Matrix Tablets Containing Combination of HPMC K100M and HPMC K15M*

F.Code	TM (mg)	HPMC K100M (mg)	HPMC K15M (mg)	MCC (mg)	PVP-K90 (mg)	IPA (mL)	MS (mg)	Talc (mg)	Total (mg)
F26	25	40	10	35.4	6	qs	1.2	2.4	120
F27	25	30	20	35.4	6	qs	1.2	2.4	120
F28	25	25	25	35.4	6	qs	1.2	2.4	120
F29	25	20	30	35.4	6	qs	1.2	2.4	120
F30	25	10	40	35.4	6	qs	1.2	2.4	120

*qs = quantity sufficient; Drug to Polymer ratio is 1:2; HPMC K100M to HPMC K15M ratio is 4:1, 3:2,1:1, 2:3, and 1:4 for F26, F27, F28, F29, and F30 respectively.

6.5. Evaluation of Precompression Blend

a) Angle of Repose

The angle of repose is the maximum angle that the plane of powder makes with the horizontal surface on rotation . Angle of repose is helpful in assessment of flow properties of particles which could be further related to packing densities and mechanical arrangements of particles.

The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation (Raghuram et al., 2003).

$$\tan \theta = h/r$$

where h = height of the powder heap

r = radius of the powder heap

θ = angle of repose

Table 13: Significance of Angle Of Repose

S.No.	Angle of repose	Flow property
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Poor

b) Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal (Lachman et al., 1987).

The bulk density and the tapped density were calculated using the following formulae.

$$\text{Bulk density} = W/V_0$$

$$\text{Tapped density} = W/V_f$$

where, W= Weight of the powder

V_0 = Initial volume

V_f = final volume

c) Compressibility Index (Carr's Index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is (Lachman et al., 1987).

$$CI = (TD-BD) \times 100/TD$$

where, TD is the tapped density and BD is the bulk density.

Table 14.Carr's Index Values

S.No.	Carr's Index	Properties
1	5-12	Free flowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

d) Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties (Lachman et al., 1987). Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index

Hausener's Ratio = Tapped density/Bulk Density

Table 15: Significance of Hausener's Ratio:

S.No	Hausner's Ratio	Property
1	0–1.2	Free flowing
2	1.2–1.6	Cohesive powder

6.6. Evaluation of Matrix Tablets

i) Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated.

ii) Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

iii) Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also.

% friability was calculated as follows

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

where W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.

iv) Weight Variation Test

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (W_A - W_I) \times 100 / W_A$$

As the total tablet weight was 120 mg, according to IP 1996, out of twenty tablets ±7.5 % variation can be allowed for not more than two tablets.

According to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

v) Drug Content (Assay)

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active ingredient in each of the 10 tested tablets lies within the range of 90% to 110% of the standard amount.

Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 100 mg of TM was transferred to a 100 mL volumetric flask containing 70 mL of 0.1N HCl. It was shaken by mechanical means for 1h.Then it was filtered through a Whatman filter paper (No. 1) and diluted to 100 mL with 0.1N HCl. From this resulted solution 1 mL was taken, diluted to 50 mL with 0.1N HCl and absorbance was measured against blank at 295 nm.

vi) In -Vitro Drug Release Characteristics

Drug release was assessed by dissolution test under the following conditions: n = 3, USP type II dissolution apparatus (paddle method) at 100 rpm in 500 mL of 0.1N HCl for first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours, maintained at 37°C ± 0.5°C. An aliquot (5mL) was withdrawn at specific time intervals and replaced with the same volume of prewarmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 295 nm.

Details of dissolution test:

Dissolution test apparatus	: USP II
Speed	: 100±0.1 rpm
Stirrer	: paddle type
Volume of medium	: 500 ml
Time interval	: 1, 2, 3,4,6,8,10 and 12 hours
Medium used	: 0.1N HCl for first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours
Temperature	: 37 ± 0.5 ^{0}C

vii) Kinetic Analysis of Dissolution Data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration (Hadjiioannou *et al*., 1993). The first order Eq. (2) describes the release from system where release rate is concentration dependent (Bourne, 2002). Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets (Hixson and Crowell, 1931).

$$C = K_0 t \quad (1)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$LogC = LogC_0 - K_1 t / 2.303 \quad (2)$$

Where, C_0 is the initial concentration of drug and K_1 is first order constant.

$$Q = K_H t^{1/2} \quad (3)$$

Where, K_H is the constant reflecting the design variables of the system.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \quad (4)$$

where, Q_t is the amount of drug remained in time t, Q_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model);

Log cumulative of % drug remaining vs. time (First order kinetic model);

Cumulative % drug release vs. square root of time (Higuchi model);

And cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law).

viii) Mechanism of drug release

Korsmeyer *et al* (1983) derived a simple relationship which described drug release from a polymeric system Eq. (5). To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model.

$$M_t / M_\infty = Kt^n \qquad (5)$$

Where $M_t / M\infty$ is fraction of drug released at time t, K is the release rate constant incorporating structural and geometric characteristics of the tablet, and n is the release exponent. The n value is used to characterize different release mechanisms.

A plot of log cumulative % drug release vs. log time was made. Slope of the line was n. The n value is used to characterize different release mechanisms as given in Table16, for the cylindrical shaped matrices. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled-drug release (Peppas, 1985).

Table 16 . Diffusion Exponent and Solute Release Mechanism for Cylindrical Shape

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case-II transport

ix) Similarity Factor (f_2) Analysis

In vitro release profiles of the selected batches (F12 and F23) of sustained release tablets were compared with the theoretical release profile which was calculated earlier. The data were analyzed by the following formula ((Bolton and Bon., 2004).

$$f_2 = 50 \log \{[1+ (1/N) \sum (R_i - T_i)^2]^{-0.5} \times 100\}$$

Where N = number of time points, Ri and Ti = dissolution of reference and test products at time i. If f_2 is greater than 50 it is considered that 2 products share similar drug release behaviors.

x) Swelling and Erosion Studies

Swelling and eroding behavior was determined by a method similar to that reported by Avachat and Vikram (Avachat and Vikram, 2007).The dissolution jars were marked with the time points of 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hours. One tablet was placed in each dissolution jar containing 500 mL of 0.1 N HCl at 37 °C ± 0.5 °C, and the apparatus was run at 100 rpm using paddle. After 2 hours, 0.1 N HCl was replaced with 500 mL of phosphate buffer pH 6.8. The tablets were taken out after completion of the respected stipulated time span as mentioned above and weighed after the excess of water at the surface had been removed with filter paper. The wetted samples were then dried in an

oven at 40 °C up to constant weight. The increase of the weight on the tablet reflects the weight of the liquid uptake. It was estimated according to following equation

$$Q = 100(W_w - W_i) / W_i$$

Where Q is the percentage swelling, and Ww and Wi are the masses of the hydrated samples before drying and the initial starting dry weight, respectively (Lopes et al., 2006).

The degree of erosion (expressed as percentage erosion of the polymer content, E) was determined using following equation.

$$E = 100(W_i - W_f) / W_i$$

where W_f is the final mass of the same dried and partially eroded sample.

xi) FTIR Studies

FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wave numbers 4000 and 400 cm^{-1}.

Xii) Stability studies of the optimized formulation:

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under influence of a variety of environmental factors such as temperature, humidity and light, and enables recommended storage conditions, re-test periods and shelf-lives to be established.

ICH specifications for stability study:

- Long term testing: $25^0C \pm 2^0C$ /60% RH ± 5% RH for 12 months.

- Accelerated testing: $40^0C \pm 2^0C$ /75% RH ± 5% RH for 6 months.

Procedure:

In the present study, stability studies were carried out at 40 ^{0}C and 75% RH for a specific time period up to 60 days for optimized formulations.

For stability study, the tablets were sealed in aluminum packaging coated inside with polyethylene. These sample containers were placed in desiccator's maintained at 75% RH.

NOTE: Saturated solution of sodium chloride at 40^0C yields a 75% relative humidity.

Evaluation of samples:

The samples were analyzed for the following parameters:

I.Physical evaluation:

Appearance: The samples were checked for any change in colour at every month.

II.Chemical evaluation:

Drug content: The samples were checked for drug content.

Drug release: The samples were subjected to drug release studies.

Chapter 7

Results

RESULTS

7.1. Standard Graph of Timolol Maleate

The standard graph of Timolol maleate ((Table. 17) has shown good linearity with R^2 values 0.9956 and 0.9968 in 0.1 N HCl (Fig. 3) and pH 6.8 buffer (Fig. 4) respectively under λmax of 295nm, which suggests that it obeys the "Beer-Lambert's law".

Table 17. Standard Graph of Timolol Maleate

Conc. (mcg/mL)	Absorbance at 295nm	
	0.1N HCl	**6.8 pH Buffer**
5	0.159	0.135
10	0.208	0.248
15	0.318	0.352
20	0.428	0.433
25	0.512	0.535
30	0.605	0.671
35	0.718	0.759
40	0.860	0.858
45	0.932	0.934
50	1.009	1.011
R^2	0.9956	0.9968

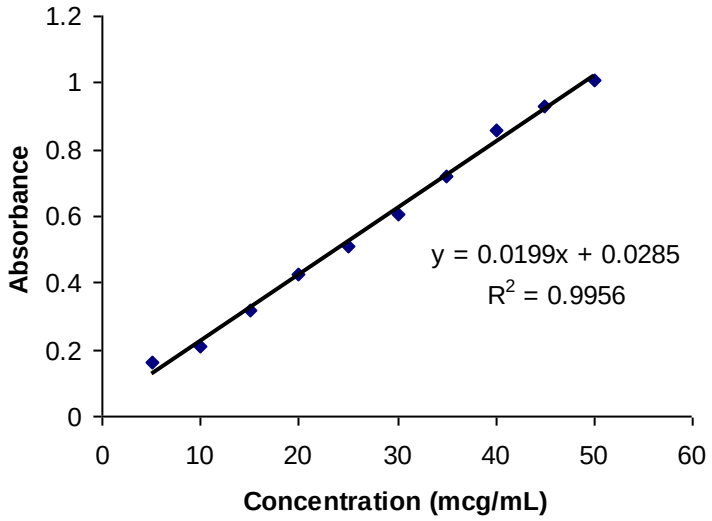


Figure 3. Standard graph of timolol maleate in 0.1 N HCl

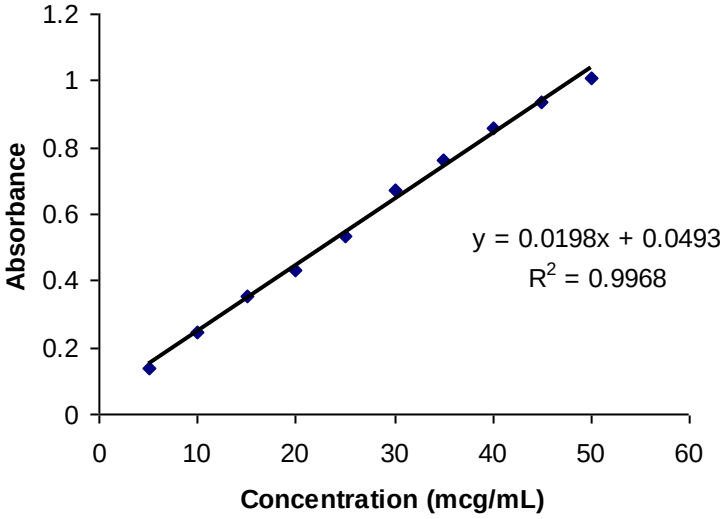


Figure 4. Standard graph of timolol maleate in 6.8 pH buffer

7.2. Dose Calculations and Theoretical Release Profile

As calculated before, the total dose required for twice-daily SR formulation of timolol maleate was found to be 25 mg and its theoretical release profile was given in Table 18.

Table 18. Theoretical Release Profile of Timolol Maleate from SR tablets

Time (hours)	Cumulative % Release
1	26.16
2	33.08
3	40
4	46.92
6	60.76
8	74.6
10	88.44
12	> 90

7.2. Characterization of Granules

The granules for matrix tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content (Table 19). Angle of repose was less than 35° and Carr's index values were less than 21 for the granules of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties. The drug content was more than 90 % for all the granules of different formulations.

Table 19. Physical Properties of Precompression Blend :

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	25.49	0.214	0.251	14.74	1.17
F2	26.24	0.308	0.364	15.38	1.18
F3	29.05	0.276	0.322	14.28	1.16
F4	26.97	0.341	0.388	12.11	1.13
F5	29.25	0.324	0.376	13.82	1.16
F6	32.27	0.320	0.397	19.39	1.24
F7	33.65	0.521	0.629	17.17	1.20
F8	33.21	0.518	0.627	17.38	1.21
F9	26.56	0.422	0.506	16.60	1.19
F10	28.75	0.481	0.572	15.90	1.18
F11	27.33	0.475	0.566	16.07	1.19
F12	25.38	0.524	0.599	12.52	1.14
F13	26.43	0.412	0.483	14.69	1.17
F14	24.77	0.488	0.537	9.12	1.10
F15	26.42	0.439	0.521	15.73	1.18
F16	28.19	0.559	0.649	13.94	1.16
F17	29.58	0.331	0.393	15.77	1.18
F18	28.73	0.362	0.428	15.42	1.18
F19	30.45	0.386	0.473	18.39	1.22
F20	26.43	0.375	0.442	15.15	1.17
F21	19.29	0.434	0.497	12.67	1.14
F22	21.25	0.520	0.582	10.65	1.11
F23	26.27	0.487	0.561	13.19	1.15
F24	25.49	0.494	0.566	12.72	1.14
F25	27.88	0.544	0.643	15.39	1.18
F26	27.34	0.510	0.591	13.70	1.15
F27	28.77	0.533	0.617	13.61	1.15
F28	28.47	0.498	0.582	14.43	1.16
F29	32.51	0.539	0.652	17.33	1.20
F30	33.17	0.482	0.589	18.16	1.22

7.3Evaluation of matrix tablets:

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 20. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 118.4 and 122.3 mg. The hardness of the tablets ranged from 5.08 to 6.16 kg/cm^2 and the friability values were less than 0.8% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 2.88 to 3.40 mm. All the formulations satisfied the content of the drug as they contained 90 to 103 % of timolol maleate and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Table 20. Physical Evaluation of Matrix Tablets

F.Code	Hardness (kg/cm^2) †	Thickness (mm) ‡	Weight (mg) ‡	Friability (%)	Drug content * (%)
F1	5.50 ±0.44	3.22±0.17	119.8±1.48	0.36	98.25±1.37
F2	5.50±0.31	3.37±0.25	120.4±0.54	0.39	95.28±0.80
F3	5.58±0.40	3.14±0.80	118.6±0.41	0.43	99.12±2.47
F4	5.66±0.55	3.20±0.20	118.8±1.64	0.12	101.22±0.88
F5	4.25±0.57	3.08±0.66	120.6±1.14	0.54	100.24±1.25
F6	4.08±0.30	3.33±0.25	119.2±0.83	0.58	99.53±1.87
F7	4.25±0.57	3.24±0.71	119.9±0.67	0.64	93.28±1.99
F8	4.41±0.60	3.32±0.89	119.0±0.43	0.37	95.35±1.14
F9	5.00±0.44	3.38±0.73	120.5±0.80	0.77	96.34±2.18
F10	5.00±0.31	3.00±0.68	121.2±0.83	0.42	91.29±0.98
F11	5.08±0.37	2.98±0.88	122.1±0.93	0.48	97.35±0.43
F12	5.41±0.70	3.11±0.36	121.2±0.97	0.15	98.88±0.88
F13	4.33±0.50	3.06±0.46	119.2±0.83	0.27	94.57±1.22
F14	4.58±0.57	2.98±0.38	122.2±0.92	0.29	90.35±2.09
F15	4.75±0.77	3.25±0.37	122.0±1.22	0.53	99.54±2.15

F.Code	Hardness (kg/cm^2) †	Thickness (mm) ‡	Weight (mg) ‡	Friability (%)	Drug content * (%)
F16	4.91±0.80	3.24±0.52	120.8±1.48	0.64	102.55±2.31
F17	5.08±0.86	3.15±0.56	118.4±1.04	0.71	93.78±1.56
F18	5.16±0.75	3.20±0.44	121.4±1.09	0.42	96.27±1.88
F19	5.25±0.67	3.11±0.55	120.7±0.65	0.66	92.55±1.56
F20	5.30±0.47	3.31±0.56	120.1±1.82	0.38	102.87±0.97
F21	5.41±0.69	2.95±0.75	122.3±0.84	0.86	100.68±1.39
F22	5.58±0.37	2.93±0.83	119.8±0.19	0.69	95.39±2.06
F23	5.66±0.65	3.33±0.59	119.8±0.38	0.37	98.90±2.31
F24	5.75±0.57	3.36±0.74	121.3±0.97	0.51	97.43±2.11
F25	6.16±0.70	3.32±0.65	122.9±0.90	0.59	97.66±2.04
F26	4.66±0.35	3.15±0.71	121.5±0.96	0.28	102.82±1.55
F27	5.08±0.37	3.26±0.43	120.2±0.76	0.35	100.44±1.21
F28	5.16±0.65	3.35±0.50	120.6±1.48	0.47	99.21±2.07
F29	5.25±0.57	3.31±0.44	120.9±0.99	0.21	91.99±2.81
F30	5.25±0.97	3.30±0.27	120.5±1.01	0.33	90.76±2.54

***** All values represent mean ± Standard Deviation (SD), n=3

† All values represent mean ± Standard Deviation (SD), n=6

‡ All values represent mean ± Standard Deviation (SD), n=20

7.4. In-Vitro Drug Release Studies

Drug Release from HPMC K15M Matrices

The results of release studies of formulations F1 to F4 are shown in Table 21 and Figure 5. The release of drug depends not only on the nature of matrix but also upon the drug polymer ratio. As the percentage of polymer increased, the kinetics of release decreased. Formulation F1 composed of drug polymer ratio of 1:0.5, failed to sustain release beyond 6h. This formulation underwent erosion before complete swelling could take place. Formulations with drug polymer ratios 1:1 (F2), 1:1.5 (F3) have extended the drug release for 8h. Further increasing the ratio to 1:2 (F4), the release was sustained for 10 h. All these formulations have shown more than 30% release in the first 1 hour indicating burst release. This phenomenon may be attributed to surface erosion or initial disaggregation of the matrix tablet prior to gel layer formation around the tablet core (Ebube et al., 1997). It is reported in the literature that more than 30% release of drug in the first hour of dissolution indicates the chance of dose dumping (Atul et al., 2006).

Table 21. In-Vitro Release Data of Timolol Maleate from HPMC K15M Matrices*

Time (hours)	F1	F2	F3	F4
1	41.94±0.87	39.96±0.93	37.12±1.22	36.78±1.53
2	53.88±0.44	50.99±0.68	50.20±0.37	48.13±1.12
3	74.58±1.10	67.43±0.49	63.09±0.96	62.99±0.84
4	82.35±1.35	80.50±1.77	77.61±0.42	75.35±0.59
6	94.28±1.79	89.47±1.35	86.23±1.49	83.30±0.97
8	-	97.55±0.21	93.83±0.74	91.15±0.68
10	-	-	-	98.47±0.81
12	-	-	-	-

*All **v**alues represent mean cumulative percent drug released ± SD (n=3)

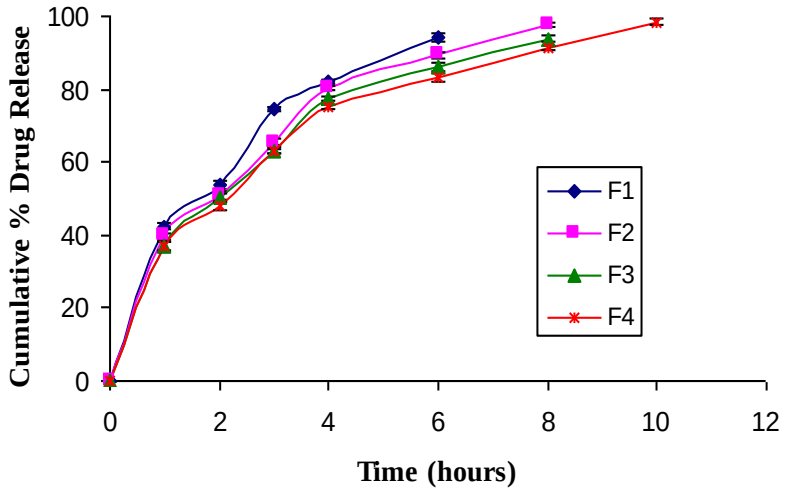


Figure 5. Release Profiles of Timolol Maleate from HPMC K15M Matrices

Drug Release from Polyethylene Oxide Matrices

High molecular weight polyethylene oxides have recently been proposed as an alternative to HPMC in controlled release matrix tablets. As shown in Table 22 and Figure 6, the drug release was extended up to 6h with initial burst release for the formulation F5. Further increase in the concentration of polymer the drug release was decreased slightly (97.19%, 92.57% and 90.77% at 8 hours for F6, F7 and F8, respectively). No burst release was observed during first hour for the formulations F6, F7, and F8 with release of 28.81%, 25.56%, and 22.38% respectively. PEO matrices have shown faster drug release compared to HPMC containing formulations. Similar findings were reported by Maggi et al., 2000. They reported that slower release rates can be obtained from the matrices containing HPMC compared to PEO.

Table 22. In-Vitro Drug Release Data of Timolol Maleate from Polyethylene Oxide Matrices*

Time (hours)	F5	F6	F7	F8
1	32.90±1.25	28.81±0.79	25.56±0.47	22.38±0.96
2	44.14±0.58	40.35±0.43	37.36±1.68	35.23±0.88
3	58.23±0.97	55.46±0.74	54.48±1.53	51.66±0.91
4	73.74±1.19	69.38±0.95	66.55±1.49	63.48±0.65
6	92.30±0.58	84.68±0.52	82.43±1.27	79.57±0.85
8	-	97.19±1.43	92.57±1.36	90.77±0.64
10	-	-	-	-
12	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3)

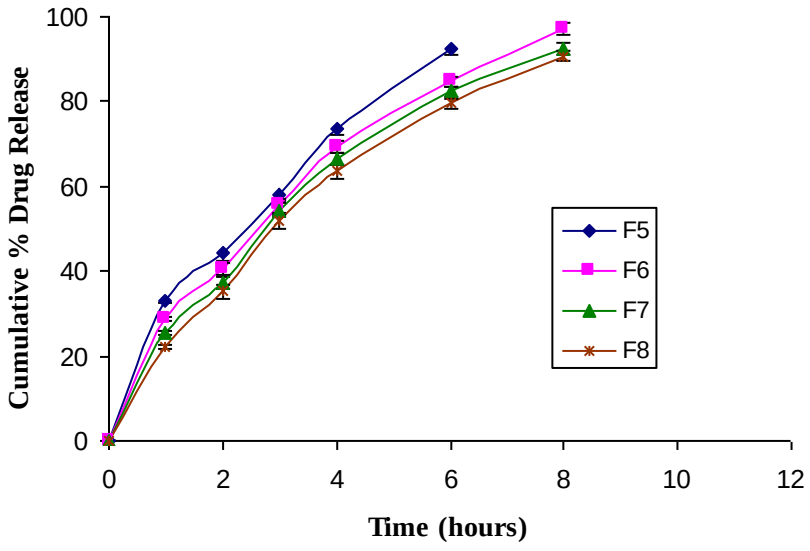


Figure 6. Release Profiles of Timolol Maleate from Polyethylene Oxide Matrices

Drug Release from HPMC K100M CR Matrices

Low molecular weight HPMC is used predominantly for tablet film coating, while high molecular weight HPMC is used as rate-controlling polymer to retard the release of drugs from a matrix at levels of 10% to 80% w/w in tablets and capsules (Raymond and Paul, 2003). Results for the drug release from HPMC K100M matrices showed in Table 23 and Figure 7. Formulations containing HPMC K100M (F9 to F12) have shown initial burst release and extended the release for 8 to 12h. As the drug polymer ratio increased to 1:2 (F12), the kinetics of release decreased (98.97% at 12h). The drug release was slower from matrices containing HPMC K100M compared to HPMC K15M. This may be due to structural reorganization of HPMC. Increase in concentration and viscosity of HPMC may result in increase in the tortuosity or gel strength of the polymer. When HPMC is exposed to aqueous medium, it undergoes rapid hydration and chain relaxation to form viscous gelatinous layer (gel layer). Failure to generate a uniform and coherent gel may cause rapid drug release (Basak et al., 2006).

Similar findings were reported by Amelia and Vikram, 2007 and Basak et al, 2006.

They revealed that 30-40% HPMC K100M was able to extend the release of water soluble drugs for more than 8 h.

Table 23. In -Vitro Release Data of Timolol Maleate from HPMC K100M Matrices*

Time (hours)	F9	F10	F11	F12
1	37.23±0.97	35.38±1.47	35.16±1.32	34.93±0.58
2	51.72±1.68	50.46±0.83	50.08±1.27	49.86±0.94
3	71.58±0.87	69.17±0.65	67.58±0.94	66.97±0.75
4	80.71±0.54	78.32±0.87	77.73±1.57	76.82±0.38
6	89.43±1.63	86.87±0.42	83.83±0.59	81.87±0.96
8	97.29±0.53	94.55±0.74	90.87±1.79	89.89±0.72
10	-	98.25±1.62	96.14±1.05	93.07±0.82
12	-	-	-	98.97±0.27

*All **v**alues represent mean cumulative percent drug released ± SD (n=3)

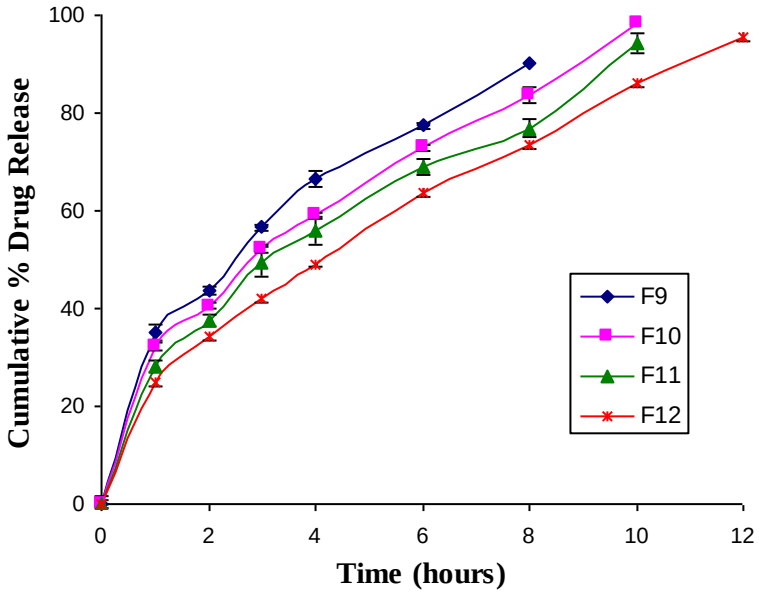


Figure 7. Release Profiles of Timolol Maleate from HPMC K100M Matrices

Drug Release from Ethylcellulose Matrices

Hydrophobic ethylcellulose can be used as a matrix former for the formulation of sustained-release dosage forms. Batches containing ethylcellulose (F13 to F16) as release retardant, extended the release up to 8 -10 hours with initial burst release. As drug polymer ratio increased, the release rate was decreased. During dissolution the erosion was observed. The results were shown in Table 24 and Figure 8.

Table 24. In-Vitro Release Data of Timolol Maleate from Ethylcellulose Matrices*

Time (hours)	F13	F14	F15	F16
1	42.27±0.57	38.7±0.82	35.62±0.71	32.42±0.62
2	52.47±0.67	47.28±0.69	46.34±0.54	42.83±0.81
3	64.86±0.73	59.73±0.87	56.84±0.37	54.86±0.42
4	77.27±0.84	74.95±0.31	72.92±0.84	68.03±1.57
6	86.63±0.79	81.62±0.64	79.72±0.53	76.26±0.46
8	98.31±0.52	96.59±0.63	94.56±0.83	85.92±0.75
10	-	-	-	97.56±0.71
12	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3)

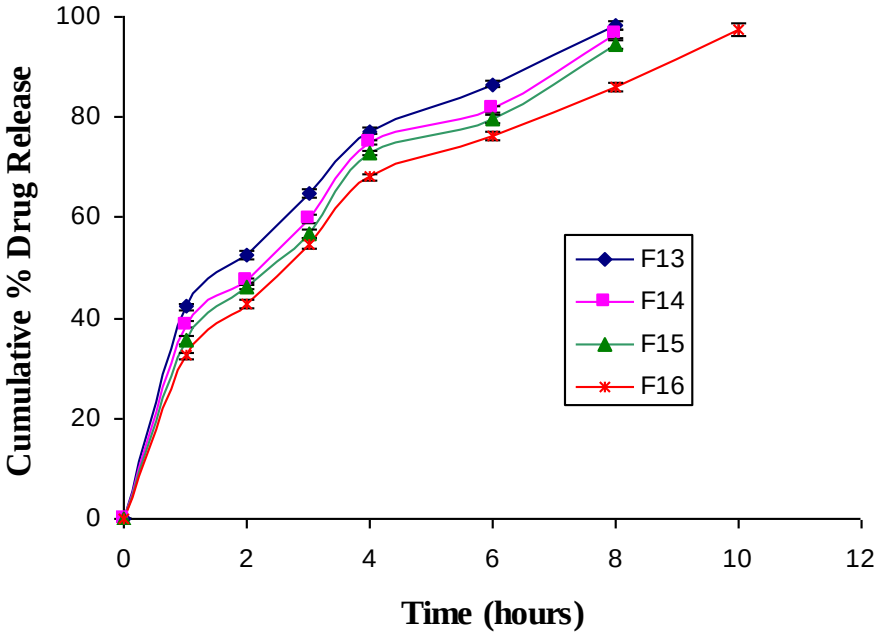


Figure 8. Release Profiles of Timolol Maleate from Ethylcellulose Matrices

Drug Release from Kollidon-SR Matrices

Kollidon-SR based formulations (F17 to F20) have shown initial burst release with sustaining the release up to 8-10 hours. The results of release studies were given in Table 25 and Figure 9.

Table 25. In-Vitro Release Data of Timolol Maleate from Kollidon-SR Matrices*

Time (hours)	F17	F18	F19	F20
1	44.24±0.83	41.09±0.73	39.72±0.88	34.84±1.37
2	55.75±0.79	52.74±0.88	48.43±0.45	42.37±0.98
3	67.26±1.80	64.89±0.62	60.93±0.61	54.93±0.74
4	77.84±0.33	75.29±1.60	72.48±0.83	67.82±0.53
6	89.34±0.86	84.73±0.57	81.76±0.74	78.05±0.71
8	97.89±0.94	94.98±0.62	92.72±0.48	89.83±0.92
10	-	-	-	97.94±0.83
12	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3)

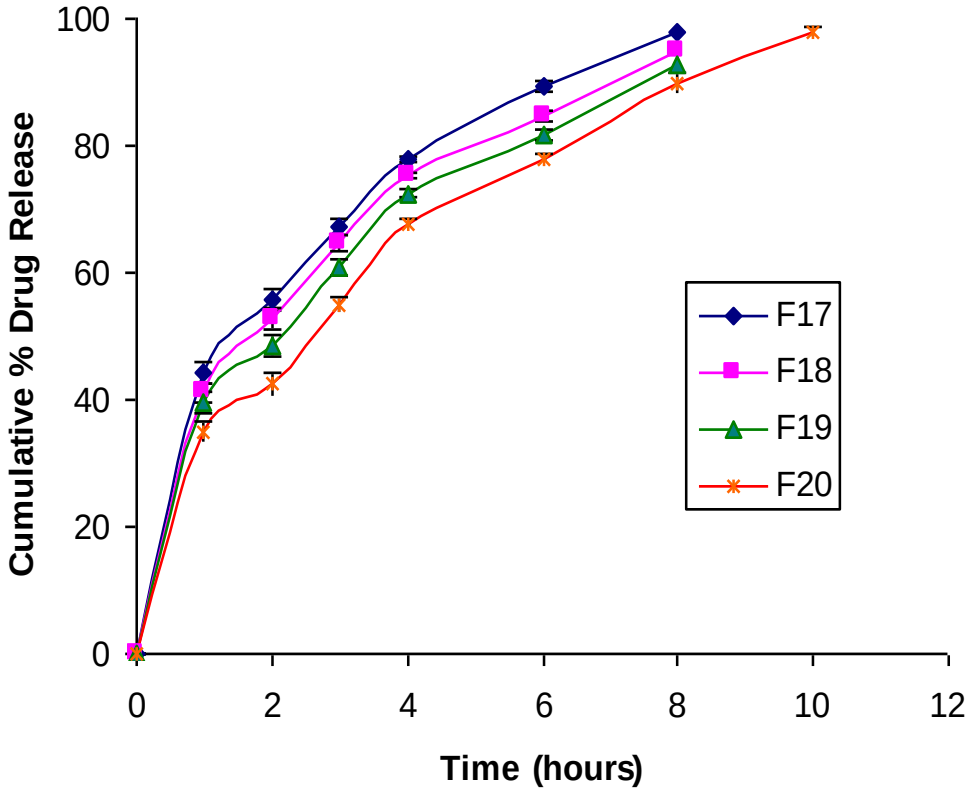


Figure 9. Release Profiles of Timolol Maleate from Kollidon-SR Matrices

Drug Release from Combination of HPMC K100M and EC Matrices

Batches containing combination of HPMC K100M and ethylcellulose (F21 to F25) have shown better release profiles (Table 26 and Figure 10). There was no burst release observed with formulations F21 to F23, and release was extended up to 10 to 12 hours. As the ethylcellulose concentration increases the drug release was decreased further in formulations F24 and F25. They prolonged the release for 8 hours only. Batch F23 was found to be optimum, as it shown similar release pattern as that of theoretical release profile.

Table 26. In -Vitro Release Data of Timolol Maleate from Tablets Containing HPMC K100M CR and Ethylcellulose*

Time (hours)	F21	F22	F23	F24	F25
1	27.06±0.85	28.73±0.97	25.38±1.54	31.86±1.37	32.23±1.15
2	40.68±0.93	42.24±0.89	35.09±1.65	44.35±1.52	47.67±1.73
3	54.27±1.29	55.85±1.17	51.93±1.69	59.83±1.46	64.83±1.58
4	66.82±1.48	66.38±1.42	62.15±1.99	70.82±1.04	75.38±1.01
6	80.72±1.79	83.35±1.73	73.88±2.01	87.43±1.96	89.25±1.90
8	88.25±1.88	90.10±1.92	81.09±2.92	94.64±1.09	98.63±0.97
10	95.17±2.38	98.43±2.05	87.04±2.48	-	-
12	-	-	97.21±2.59	-	-

*All **v**alues represent mean cumulative percent drug released ± SD (n=3)

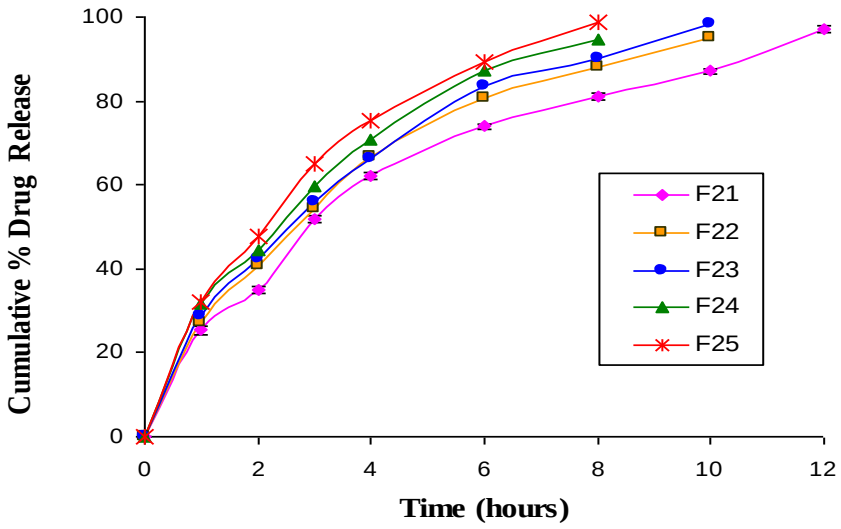


Fig. 10. Release Profiles of Timolol Maleate from Tablets Containing HPMC K100M CR and Ethylcellulose

Drug Release from Combination of HPMC K100M and HPMC K15M Matrices

Combination of HPMC K100M and HPMC K15M was extended the release for 10 hours. No significant change in the drug release was observed with changing the ratio of polymers. All the batches (F26 to F30) have shown burst release also. Data was given in Table 27 and Figure 11.

Table 27. In-Vitro Release Data of Timolol Maleate from Tablets Containing HPMCK100M and HPMC K15M*

Time (hours)	F26	F27	F28	F29	F30
1	31.25±0.83	32.82±0.95	32.86±0.64	33.55±0.86	34.20±0.38
2	38.28±0.76	42.71±0.88	44.83±0.58	45.91±0.77	47.04±0.46
3	53.88±0.58	56.36±0.72	57.73±0.37	59.45±0.73	61.37±0.39
4	66.46±0.87	67.83±0.46	69.38±0.74	71.24±0.56	74.27±0.48
6	74.25±0.56	76.25±0.55	76.54±0.83	79.83±0.49	81.38±0.64
8	83.89±0.58	85.93±0.74	86.25±0.57	88.28±0.68	89.36±0.56
10	90.63±0.63	93.06±0.67	95.84±0.68	96.09±0.47	97.23±0.84
12	-	-	-	-	-

*All values represent mean cumulative percent drug released ± SD (n=3)

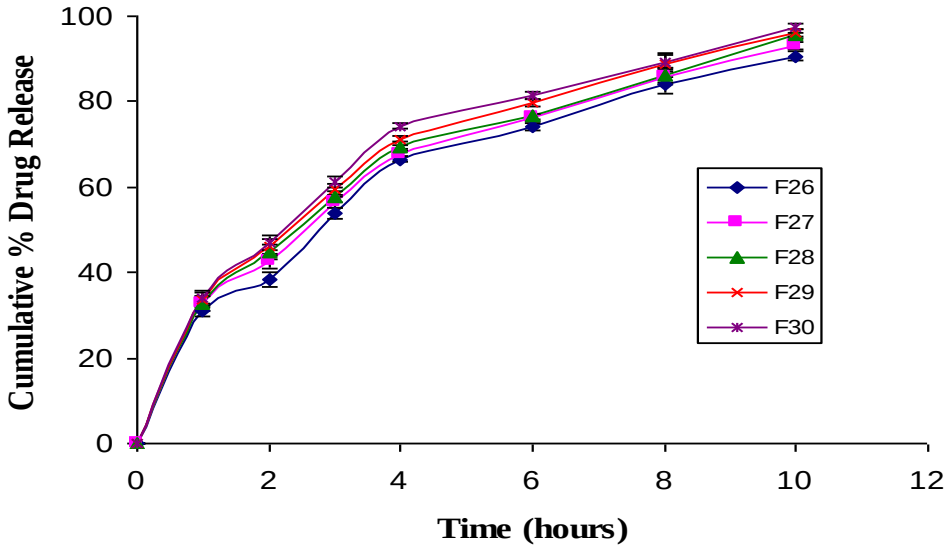


Figure 11. Release Profiles of Timolol Maleate from Tablets Containing HPMCK 100M and HPMC K15M

Out of total 30 batches, the drug release was extended up to 12 hours for the formulations F12 and F23. So, these two formulations selected for further studies like kinetic data analysis and similarity factor analysis.

Kinetic analysis of dissolution data

The release rate kinetic data for the F12 and F23 is shown in Table 30 and Table 31 respectively. As shown in Figures 14-18, drug release data was best explained by first order equation, as the plots showed the highest linearity (r^2 = 0.9955), followed by Hixson-Crowell (r^2 = 0.9800) and Higuchi's equation (r^2 = 0.9661). As the drug release was best fitted in first order kinetics, indicating that the rate of drug release is concentration dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. The applicability of the formulation to the Hixson –Crowell cube root law indicated a change in surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time.

Mechanism of drug release

As shown in Figure 17, the corresponding plot (log cumulative percent drug release vs time) for the Korsmeyer-Peppas equation indicated a good linearity (r^2 = 0.9741). The diffusion exponent n was 0.66, which appears to indicating a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and may indicate that the drug release was controlled by more than one process.

Table 28.Drug Release Kinetics of Batch (F12) Matrix Tablets*

Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
r^2	K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	K_{HC} ($h^{-1/3}$)	r^2	n	K_{KP} (h^{-n})
0.8461	5.188	0.8665	0.1890	0.9335	24.877	0.9695	0.2461	0.9911	0.56	0.4283

* r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

Table 29.Drug Release Kinetics of Optimized (F23) Matrix Tablets*

Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
r^2	K_0 (h^{-1})	r^2	K_1 (h^{-1})	r^2	K_H ($h^{-1/2}$)	r^2	K_{HC} ($h^{-1/3}$)	r^2	n	K_{KP} (h^{-n})
0.8985	5.881	0.9955	0.2012	0.9661	27.839	0.9800	0.1997	0.9741	0.66	0.3238

* r^2 = Correlation coefficient; K = Kinetic constant; n= Diffusional exponent.

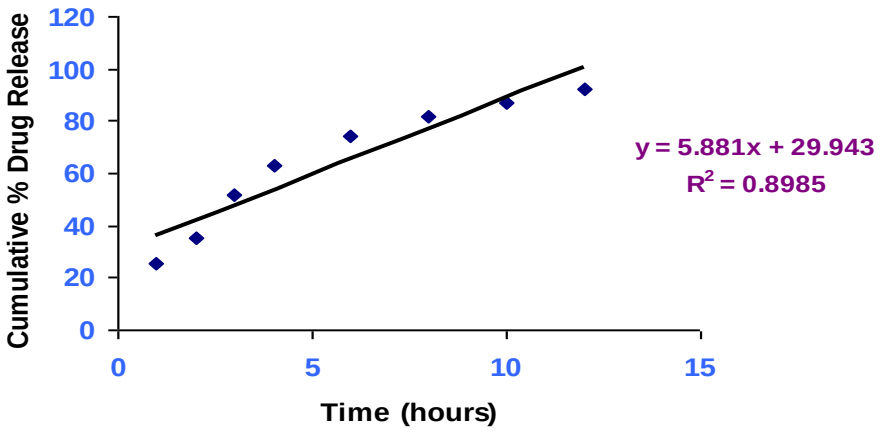


Figure 12. Zero Order Graph of Optimized Formulation (F23)

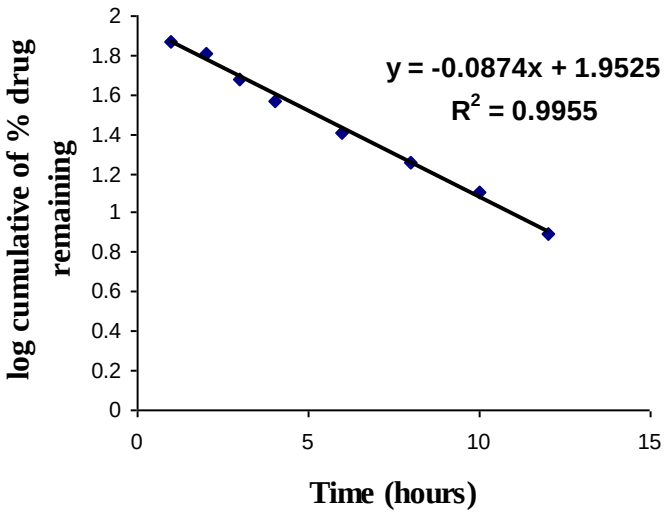


Figure 13. First Order Graph of Optimized Formulation (F23)

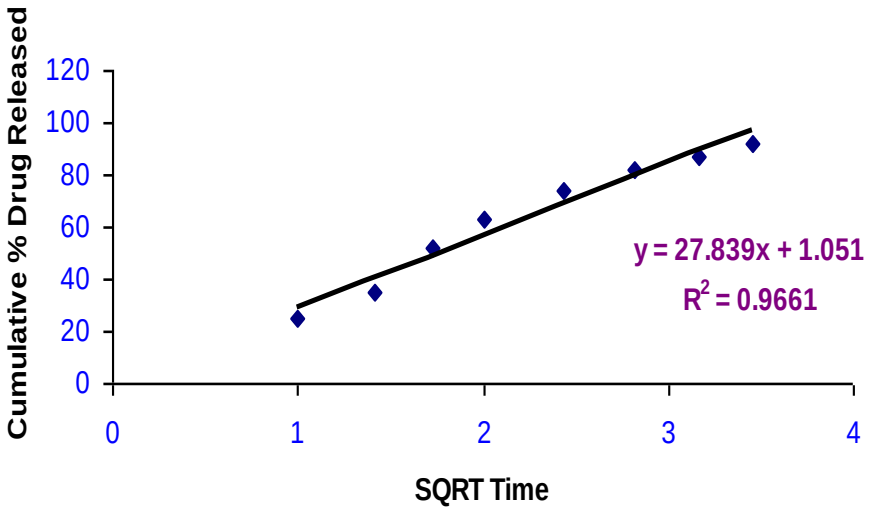


Figure 14. Higuchi Plot of Optimized Formulation (F23)

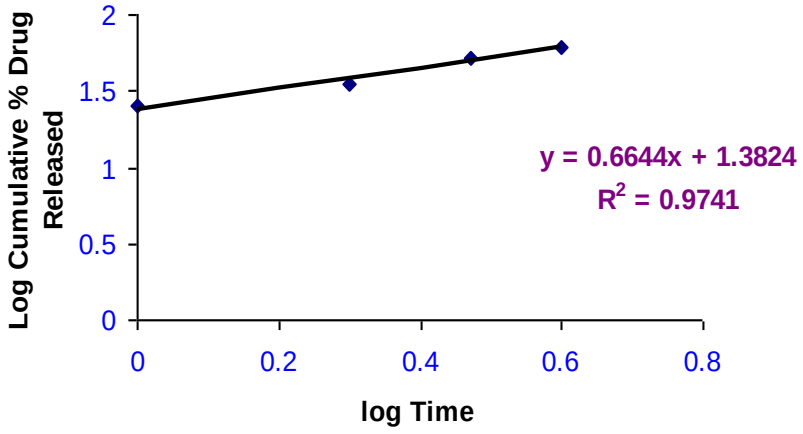


Figure 15. Korsmeyer-Peppas Graph of Optimized Formulation (F23)

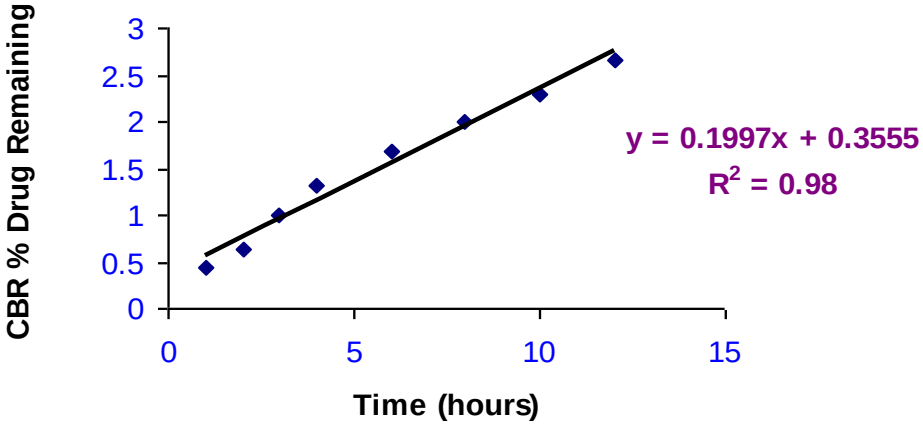


Figure.16:Hixson-Crowell Plot of Optimized Formulation (F23)

Similarity factor analysis

Similarity factor results for the batches F12 and F23 were given in Table 32. Similarity factor analysis between F23 tablets and theoretical release has shown an f_2 factor greater than 50 at each time point with an average value of f_2 factor 80.18. Incase of F12 tablets, an average value of f_2 factor was greater than 50, but at the 3rd and 4th hours f_2 factor was less than 50.

The in-vitro release behaviour of F12, F23 batches of tablets were compared with the theoretical release profile. A close relationship was observed between F23 formulation and theoretical release patterns, compared to a relationship between F12 and theoretical release patterns (Figure 19).

So, F23 was considered as optimized formulation, as these tablets did not show any burst release and extended the release for 12 hours with similar release pattern to that of theoretical release profile.

Table 30. Similarity Factor Analysis

	Average % Drug Release			*f2 factor*	
Time (hrs)	**Theoretical release**	**F12**	**F23**	**F12**	**F23***
1	26.16	34.93	25.38	73.03	99.09
2	33.08	49.86	35.09	59.62	95.05
3	40.00	66.97	51.93	49.47	66.77
4	46.92	76.82	62.15	47.25	61.66
6	60.76	81.87	73.88	64.79	64.79
8	74.60	89.89	81.09	54.73	78.84
10	88.44	93.07	87.04	61.58	97.31
12	99.00	98.07	97.21	66.72	77.99

* Average value of *f2* factor = 80.18

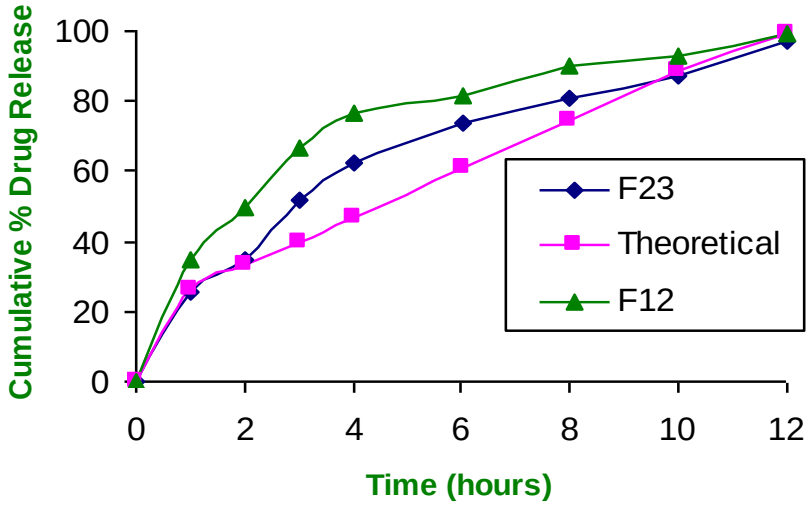


Figure 17. Comparative In-Vitro Drug Release Profile

Swelling and erosion behaviour, FTIR studies, and stability study were performed on optimized formulation (F23).

Determination of swelling and eroding behavior

Since the rate of swelling and erosion is related and may affect the mechanism and kinetics of drug release, the penetration of the dissolution medium and the erosion of the hydrated tablets were determined. Simultaneously with the swelling study, the percentage erosion of polymer was determined. The percentage swelling and erosion of optimized tablet was shown in Figures 20 and 21, and data was given in Table 33. Maximum swelling was observed in first 2 hours and gradually it was decreased with simultaneous erosion of polymer.

Table 31. Swelling and Erosion Study of Optimized Formulation (F23)

Time (hours)	% Swelling	% Erosion
1	76.43	18.72
2	128.35	24.37
3	84.57	28.73
4	71.94	42.62
6	60.64	56.83
8	49.53	64.52
10	36.72	72.41
12	24.83	93.29

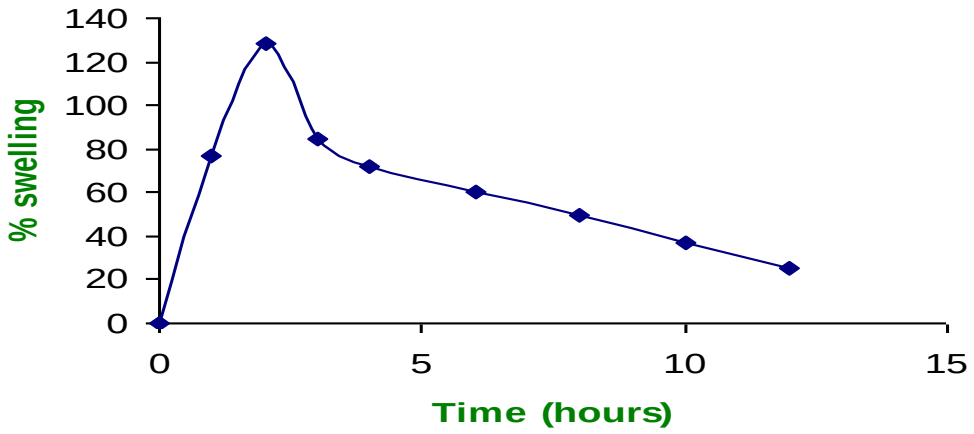


Figure 18. Swelling Study of Optimized Formulation (F23)

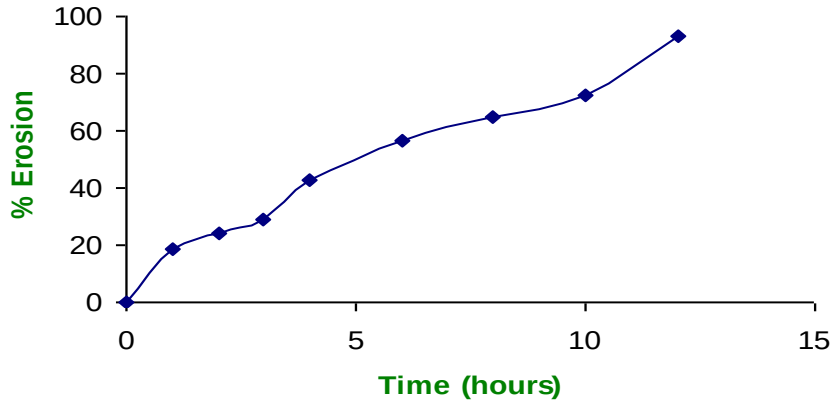
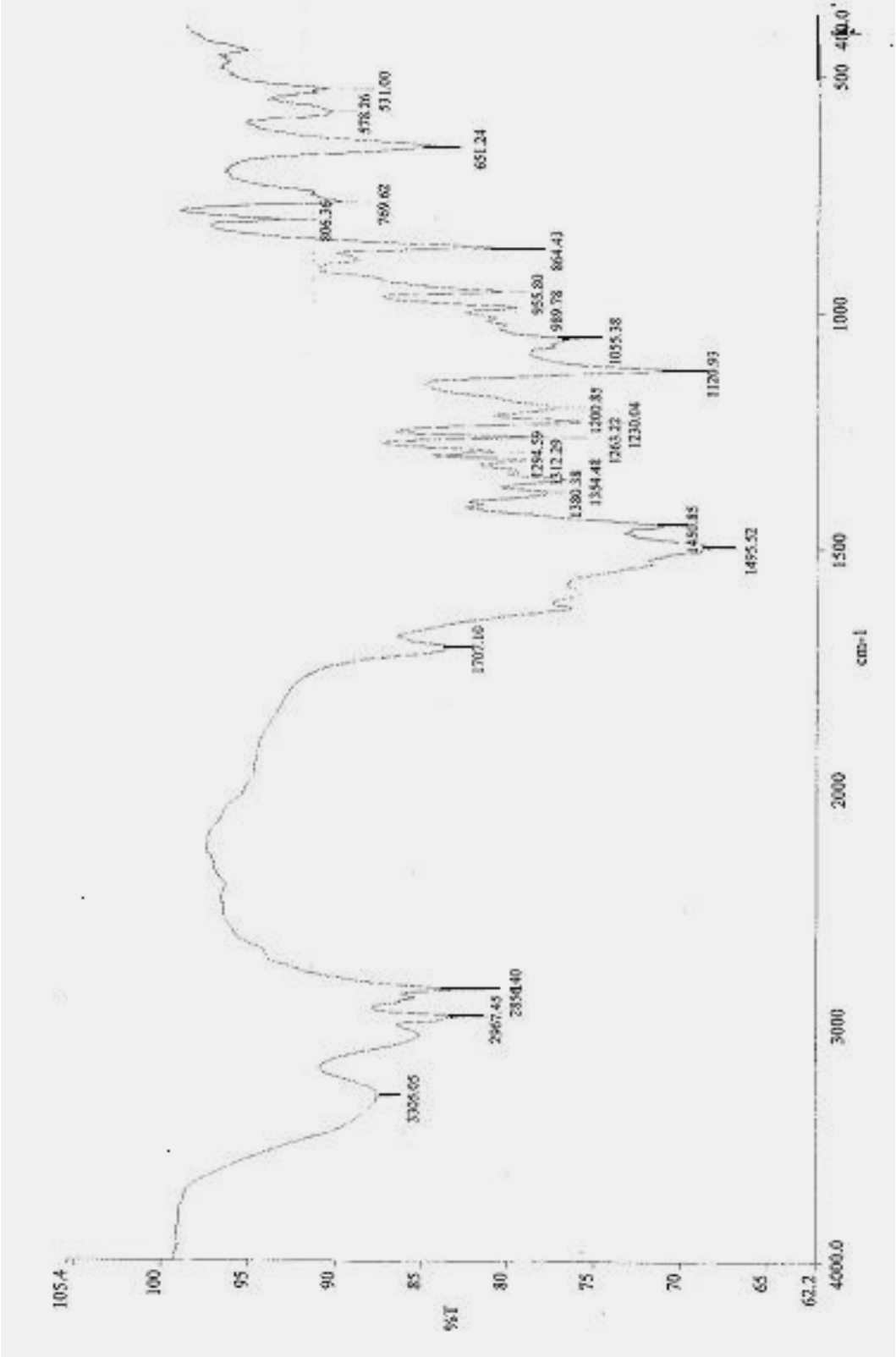


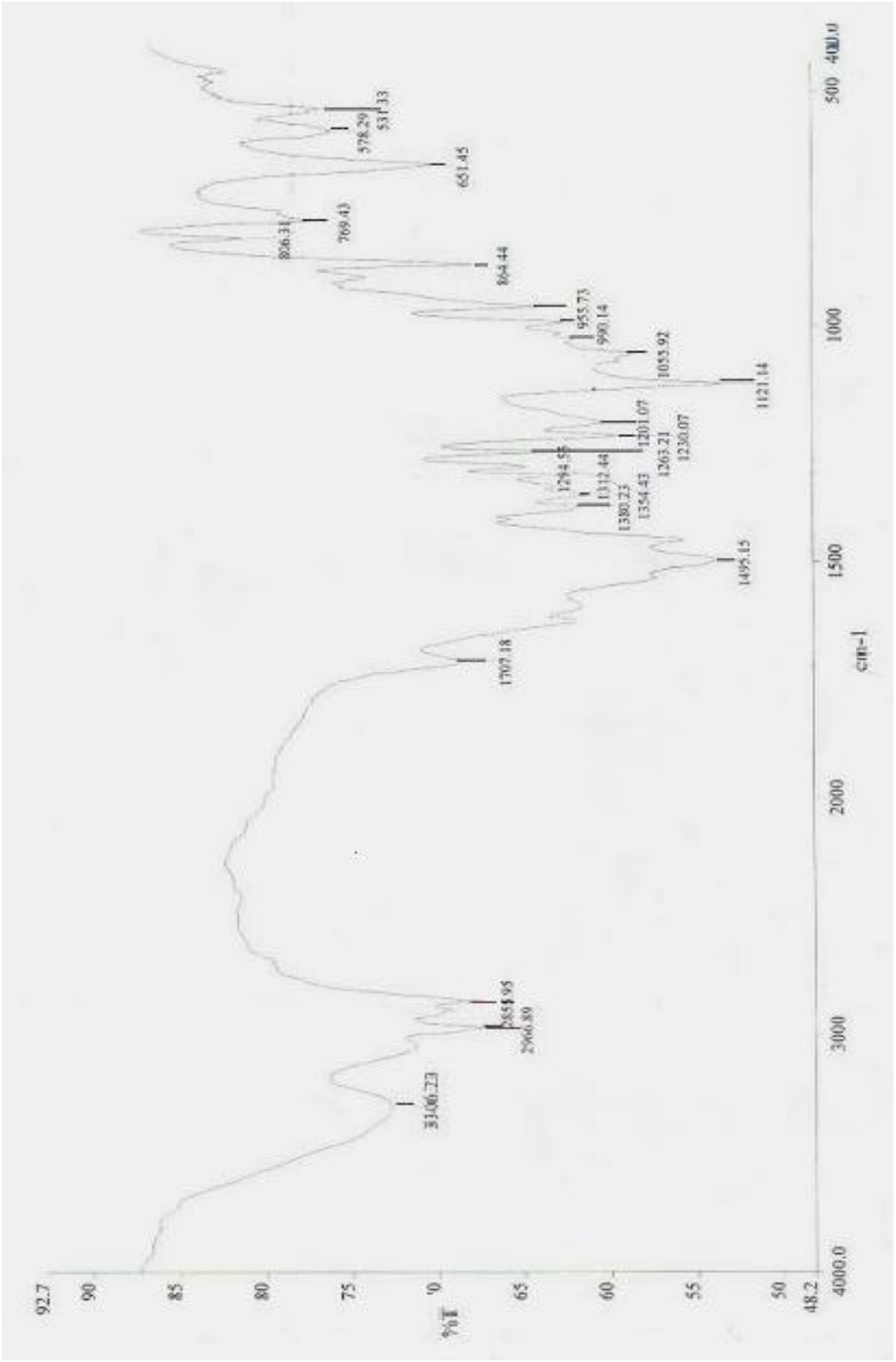
Figure 19. Erosion Study of Optimized Formulation (F23)

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the drug and the optimized formulation were recorded in range of 4000-400 cm^{-1}. Timolol maleate showed some prominent and characteristic peaks. The peaks at 3305 and 1120 cm^{-1} were due to stretching vibrations of O-H and C-O bond of secondary alcohol respectively. Peaks at 2967, 2856, and 1707 cm^{-1} could be assigned to the asymmetric C-H stretching of CH_3 group, symmetric C-H stretching of CH_2 group, and C=N stretching respectively. In the optimized formulation, the presence of all the characteristic peaks of the timolol maleate indicates that no interaction was occurred between the drug and the excipients.



FTIR spectrum of Timolol Maleate



FTIR Spectrum of optimized formulation(F23)

ACCELERATED STABILITY STUDIES

The optimized batch of F23 Timolol maleate matrix tablet 120 mg were evaluated for accelerated stability studies at 40^0C / 75 % RH condition. The stability details / results are presented as below.

The stability studies on Timolol maleate matrix tablet 120 mg in HDPE container at 40^0C / 75 % RH for 2 months were conducted as per ICH protocol. After the specified time period (1 month and 2 months), the samples were unloaded from the stability chambers and were tested for any physical or chemical changes. Also the tests for dissolution and assay were conducted to assess the stability of product.

Storage Condition: 40^0C / 75 % RH

Pack: HDPE Container

Storage Period: 1 month and 2 months

Stability studies were carried out for optimized formulation they had showed good stability and the values were within permissible limits and the values are tabulated below

Table no.32 Accelerated stability studies data:

S.No	Test	Specifications	Initial	After 1 month	After 2 months
1	Description	White/Off-white coloured tablets	Complies	Complies	Complies
2	Identification	The retention time of major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay.	Complies	Complies	Complies
3	Dissolution (In purified water)	NLT 80% release after 12 hours	98.3%	97.8%	97.5%
5	Assay (By uv)	NLT 95.0 percent and NMT 105.0 percent	99.16%	98.77%	98.69%

The results for dissolution and assay are summarized below.

Dissolution:

No significant change was observed in the percentage drug dissolved after a storage period of 1 month at 40^0C / 75 % RH and 2 months at 40^0C / 75 % RH for Timolol maleate matrix tablet 120 mg.

Tabel:20

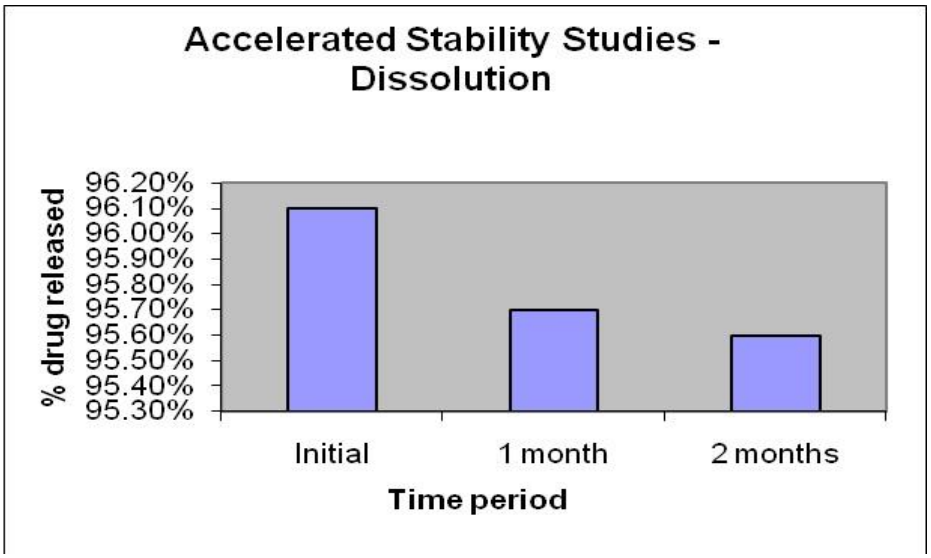
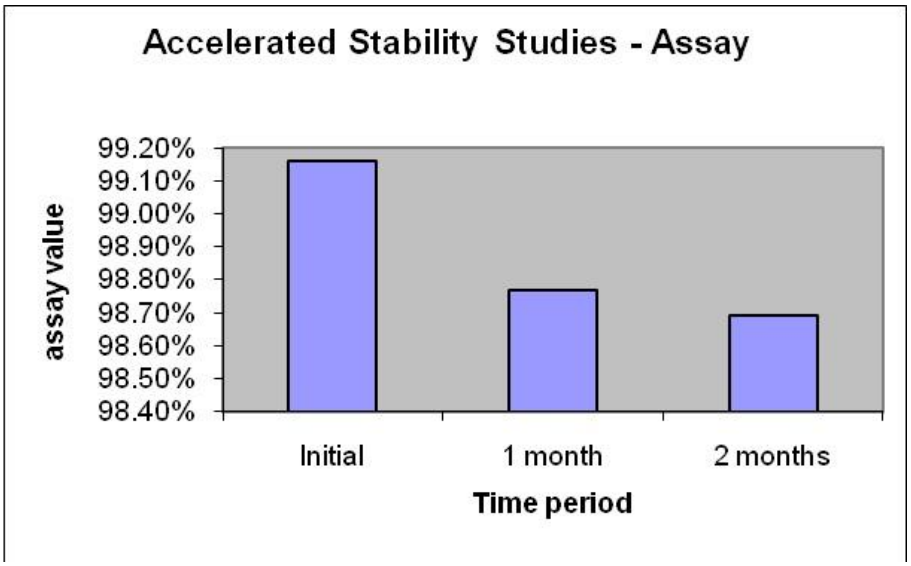


Fig 8.13 - Accelerated stability studies – Dissolution

Assay:

No significant change was observed in the assay value of Timolol maleate matrix tablet 120 mg, after a storage period of 1 month at 40^0C / 75 % RH and 2 months at 40^0C / 75 % RH.

Tabel:21



Inference:

From the above data it was evident that there was no significant change in the physical and chemical parameters of Timolol Maleate matrix tablet during the stability studies conducted at 40°C & 75%RH for1 month period and 2 months at 40°C & 75%RH.

Chapter 8

Discussion

DISCUSSION

Oral drug delivery system represents one of the frontier areas of controlled drug delivery system; such dosage forms are having a major advantage of patient compliance. The Extended release dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form.

A controlled release matrix dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent used for the treatment of Hypertension. The therapeutic concentration required for this purpose is 20-40mg/day. The therapeutic dose is needed to be maintained for 12 hrs. The conventional doses release the entire drug in just few minutes and therefore the therapeutic concentrations are maintained for a short period of time generating a need for administration of another dose. Therefore a sustained release formulation of timolol maleate which would release the drug over a time period of 12 hrs is beneficial.

The objective of the study is to formulate and evaluate Timolol maleate extended release matrix tablets. To enhance the release, an attempt was made to prepare the controlled release matrix tablet using polymers such as HPMC K15 M, Polyethylene Oxide, Ethyl Cellulose, Kollidion-SR , and HPMC K100M.

Hence, the present research work was to study systematically the effect of formulation variables on the release of Timolol maleate.

PREFORMULATION PARAMETERS:

Determination of λ_{max} of Timolol maleate:

On the basis of preliminary identification test it was concluded that the drug complied the preliminary identification. From the scanning of drug, it was concluded that the drug had λ_{max} of 295 nm, which was equal to 295 nm as reported. Also, an IR spectrum was concordant with the reference spectrum of Timolol maleate.

Preparation of standard calibration curve of Timolol maleate:

From the standard curve of Timolol maleate (Table No. 17, Graph 3), it was observed that the drug obeys beer's law in concentration range of 5 – 50 µg/ml in 0.1N HCL and phosphate buffer ph 6.8. The linear regression equation generated was used for the calculation of amount of drug.

Determination of IR spectrum of Timolol maleate:

Physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference in the functional group as the principle peaks of the Timolol maleate were found to be unaltered in the drug-polymer physical mixture, indicating they were compatible chemically.

DRUG EXCIPIENT COMPATABILITY STUDIES

Drug-Excipient compatibility studies form an important part of Preformulation studies for the determination of interaction between drug and excipient. It is determined after storage of specific time period by using suitable analytical techniques and the results are indicating that there is no interaction between drug and excipients.

FORMULATION DESIGN:

Formulation of the controlled release matrix tablet:

The use of hydrophilic polymers is currently the most applied method in controlling the release of drugs from oral pharmaceutical dosage forms. Hydroxypropylmethylcellulose (HPMC) is a polymer frequently used in formulation of controlled release devices, for its ability to form rapidly a gel layer at the matrix periphery exposed to aqueous media. The difference in the molecular weight and viscosity of HPMC polymer influence the release of the drug.

Kollidion-SR, Ethyl cellulose and polyethylene oxide are used as polymers for the extended release of the drug

Microcrystalline cellulose and lactose are used as the tablet diluent and binding agent.

2 % of Magnesiumsterate added in extra granular as a lubricant.

EVALUATION PARAMETERS:

Physicochemical evaluation:

The prepared tablets were subjected to preliminary characterization such as hardness, thickness, % weight variation, friability and drug content. The evaluated parameters were within acceptable range for all the formulations. The values are indicated in Table No. --.

Table No. 43: Range for value of preliminary characterization of formulations

Parameters	Range
Hardness (kg/cm^2)	4.08±0.8 – 6.16±0.7
Thickness (mm)	2.95 ± 0.75 – 3.32 ± 0.65
Weight variation (%)	118.6±0.41 – 122.9±0.9
% Friability	0.12 - 0.77
Drug content (%)	90.35 – 102.87

In vitro drug release profile:

The dissolution test for in vitro release of all the formulation , were carried out using USP Type –II(paddle).A revolving at 100 rpm with phosphate buffer pH -6.8 dissolution media was used. The study carried out at 37±0.5° drug release as shown in tables from

The results are described as:

The formulations F1, F2, F3 and F4 are formulated with different concentrations of HPMCK15M with 1:0.5,1:1,1:1.5 and 1:2 respectively. And the release of the drug was faster. In all these formulations 90% of the drug release was with in 10 hours. the desired f2 value was not achieved.

The formulations F5, F6, F7 and F8 are formulated with different concentrations of Polyethylene Oxide with 1:0.5,1:1,1:1.5 and 1:2 respectively. And the release was highly sustaining as the concentration of the polymer is increasing. In all these formulations the release was more than 97% at the end of the 8th hour. And the desired f2 values are not achieved.

The Formulations containing HPMC K100M (F9 to F12) have shown initial burst release and extended the release for 8 to 12h. As the drug polymer ratio increased to 1:2

(F12), the kinetics of release decreased (98.97% at 12h). The drug release was slower from matrices containing HPMC K100M compared to HPMC K15M. This may be due to structural reorganization of HPMC. Increase in concentration and viscosity of HPMC may result in increase in the tortuosity or gel strength of the polymer. The desired f2 values are not achieved.

The formulations containing ethylcellulose (F13 to F16) as release retardant, extended the release up to 8 -10 hours with initial burst release. As drug polymer ratio increased, the release rate was decreased. During dissolution the erosion was observed.

The formulations containing Kollidon-SR b (F17 to F20) have shown initial burst release with sustaining the release up to 8-10 hours. The release is 95.04% at 10 hrs and desired f2 values are not obtained.

The formulations containing combination of HPMC K100M and ethylcellulose (F21 to F25) have shown better release profiles. There was no burst release observed with formulations F21 to F23, and release was extended up to 10 to 12 hours. As the ethylcellulose concentration increases the drug release was decreased further in formulations F24 and F25. They prolonged the release for 8 hours only. Batch F23 was found to be optimum, as it shown similar release pattern as that of theoretical release profile.

The formulations containing combination of HPMC K100M and HPMC K15M(F26 to F30) was extended the release for 10 hours. No significant change in the drug release was observed with changing the ratio of polymers. All the batches have shown burst release also.

DATA ANALYSIS:

The curve fitting results of the release rate profile of the designed formulations gave an idea on the mechanism of drug release.

Based on the "n" values are ranging from0.56-0.66 for all the formulations formulation, the drug release was found to follow Anomalous (non-Fickian) diffusion. This value indicates a coupling of the diffusion and erosion mechanism (Anomalous diffusion) and indicates that the drug release was controlled by more than one process.

Also, the drug release mechanism was best explained by zero order, as the plots showed the highest linearity (r^2 = 0.8985), As the drug release was best fitted in zero order kinetics, it indicated that the rate of drug release is concentration independent.

Criteria for selection of optimized formulation:

Similarity factor analysis between F23 tablets and theoretical release has shown an f_2 factor greater than 50 at each time point with an average value of f_2 factor 80.18. Incase of F12 tablets, an average value of f_2 factor was greater than 50, but at the 3rd and 4th hours f_2 factor was less than 50.

The in-vitro release behaviour of F12, F23 batches of tablets were compared with the theoretical release profile. A close relationship was observed between F23 formulation and theoretical release patterns, compared to a relationship between F12 and theoretical release patterns.

So, F23 was considered as optimized formulation, as these tablets did not show any burst release and extended the release for 12 hours with similar release pattern to that of theoretical release profile.

Hence the above said formulations were selected for further evaluation such as accelerated stability studies.

Stability Studies:

Stability studies were carried out for optimized formulation they had showed good stability and the values were within permissible limits.

Chapter 9

Summary and Conclusion

SUMMARY AND CONCLUSION

Summary:

Timolol maleate is a nonselective beta-adrenergic receptor blocking agent. It possesses an asymmetric carbon atom in its structure and is provided as the levo isomer.

As the conventional doses release the Timolol maleate in just few minutes and therefore the therapeutic concentrations are maintained for a short period of time generating a need for administration of another dose

Therefore an attempt is made to maintain the therapeutic concentration for longer period of time. This is achieved by developing controlled release drug delivery system. These controlled release matrix tablets mainly prepared for release of the drug for longer period of time i.e., 12 hours and utilizing the drug to full extent avoiding unnecessary frequency of dosing.

For the formulation of controlled release matrix tablet HPMC K 15M , HPMC K100M,Ethyl cellulose, PVP, Kollidion-SR was used as matrix forming agents. Other excipients used are microcrystalline cellulose and lactose(diluents), Magnesium stearate (lubricating agent). Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions.

The prepared controlled release tablets were evaluated for hardness, Weight variation, thickness, friability, drug content uniformity, In-vitro dissolution studies. F23 formulation showed good evaluation studies and a controlled drug release. The dissolution profiles of all the formulations are compared with theoretical values by calculating the f2 values. F23 has obtained the highest f2 value (77.99) hence F23 is considered to be the optimized formulation. Stability studies were carried out for F23 formulation and they had showed good stability when stored at accelerated stability state as per the ICH guideline and the values were with in a permissible limits.

Matrix tablets were compressed without any problem and do not require any change in ratio of excipients in formulation. Results of the present study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained-release matrix tablets of timolol maleate.

All the formulations containing drug to polymer ratio 1:2 and MCC as a diluent extended the drug release for 8 to 12 hours. Lactose containing formulations have shown faster drug release.

Among the hydrophilic matrix formers, the rate of drug release was in the following order

PEO > HPMC K15M > HPMC K100M.

PEO containing formulations (F6-F8) have did not show initial burst release.

The drug release rate was almost similar with hydrophobic EC and plastic Kollidon-SR.

The drug release rate was slower with the tablets containing combination of both hydrophilic HPMC K100M and hydrophobic EC polymers compared to with that of combination of 2 hydrophilic polymers (HPMC K100M and K15M).

Compared to direct compression, wet granulation method was found to be better choice to extend the drug release for 12 hours.

Majority of formulations have released the drug by non-Fickian diffusion.

Erosion was the dominating release mechanism for the formulations containing Kollidon-SR or EC.

It was observed that Formulations F23 retained the drug release up to 24 hrs. All formulations were subjected for four different models viz. Zero order, First order, Higuchi matrix and Peppas model equations and all the formulations best fit in to the Peppas model by giving the values of diffusional exponent (n) in the range of 0.56-0.66 that indicate the formulation had release the drug by diffusion followed by erosion mechanism.

It was revealed that polymers and lactose ratios had significant influence on drug release. Thus it is summarized that stable dosage form can be developed by timolol maleate for sustained release matrix tablets.

Conclusion:

The aim of the present study was to develop an controlled release formulation of Timolol maleate to maintain constant therapeutic levels of the drug for over 12 hrs.

Timolol maleate controlled release matrix tablets are prepared by wet granulation method with different grades of HPMC.

An efficient extended release formulation of Timolol maleate could be designed as controlled release tablets. The optimised formulation (F23) was developed by using HPMC K100M and Ethyl cellulose(1:1).

The results of dissolution studies indicated that formulation F-23, the most successful of the study, exhibited drug release pattern very close to theoretical release profile. The designed matrix tablets F-23 of timolol maleate, which release 25.38% respectively of drug in the first hour and extend the release upto 12 hours, can overcome the disadvantages associated with conventional tablets formulation of Timolol Maleate tablets. Regulated drug release in zero order kinetics attained with this formulation.

The release process involves anomalous diffusion mechanism or diffusion coupled with erosion, as indicated by the n value of 0.66 in Korsmeyer's plot. There was an alteration in the surface area and diameter of the tablets with the progressive dissolution of the matrix as a function of time, as indicated in Hixson-Crowell plot. FTIR studies combined with stability studies proved the integrity of the developed matrix tablets.

Hence it can be concluded that twice a daily controlled release matrix tablet of Timolol maleate having satisfactory extended release profile which may provide an increased therapeutic efficacy. The developed formulation overcome and alleviates the drawback and limitation of extended release preparations.

Chapter 10

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